Exploiting the peri effect in thia-substituted napthalenes

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Exploiting the *Peri* Effect in Thia-Substituted Naphthalenes

A thesis submitted for the degree of

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by

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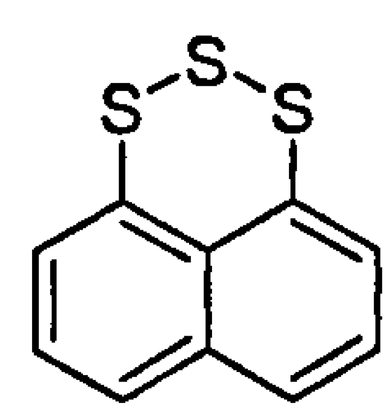
ABSTRACT

The cyclic trisulfide and trisulfide oxide A and B are strained systems as a consequence of their fusion to the *peri*-positions of a naphthalene ring. Release of ring strain is anticipated to be a driving force in their controlled decomposition to small molecular fragments of synthetic interest. The former has been investigated as a reagent for the direct conversion of alkenes to episulfides. The latter has been found to be an efficient sulfur monoxide transfer reagent in trapping experiments with dienes.



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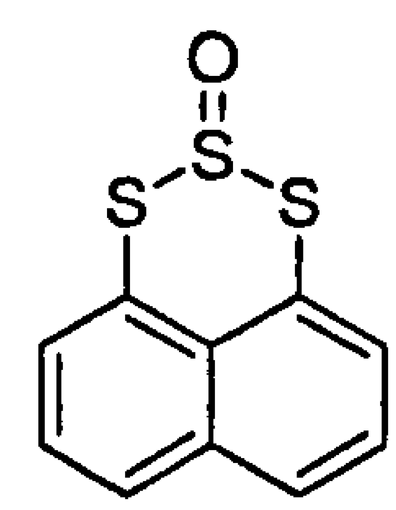
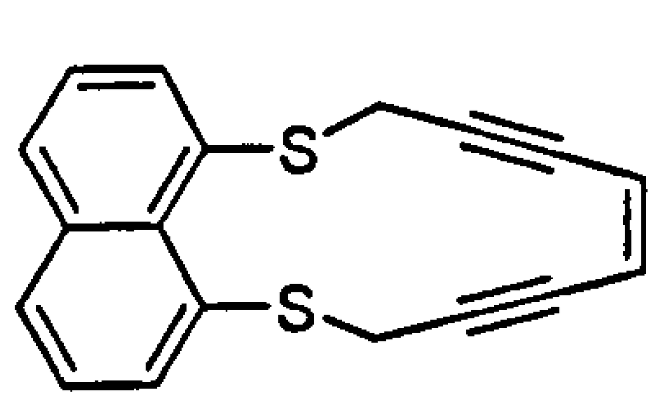


B

A series of novel macrocyclic sulfur-containing enediynes C-L have been synthesised. Their susceptibility to undergo the Bergman cyclisation to reactive 1,4-dehydrobenzene diradicals has been analysed by differential scanning calorimetry and rationalised on the basis of structural considerations and computational results.



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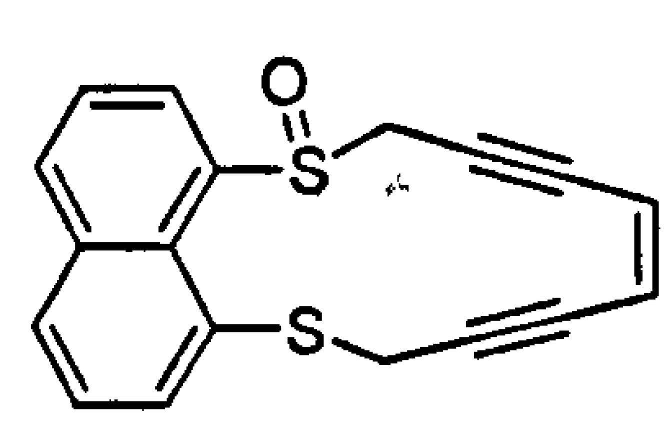

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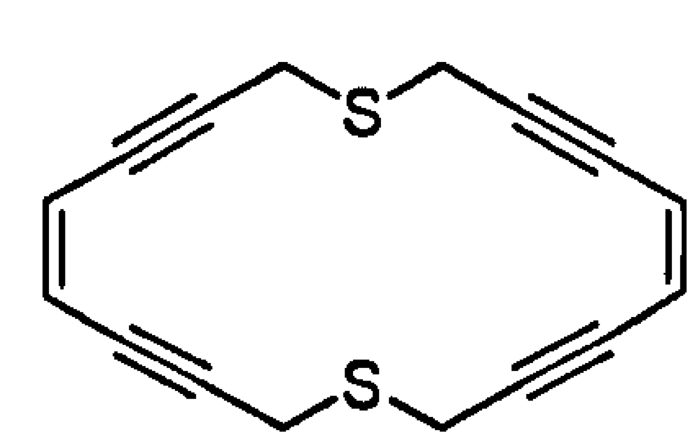

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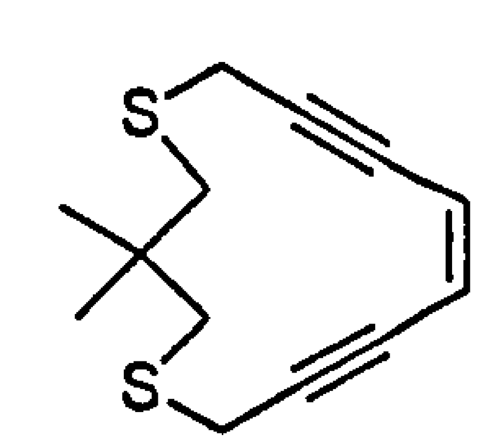

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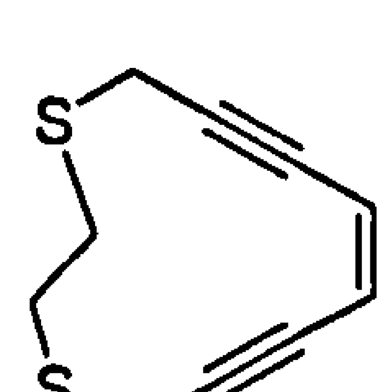

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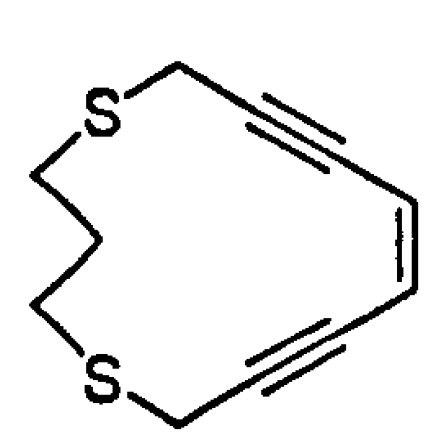

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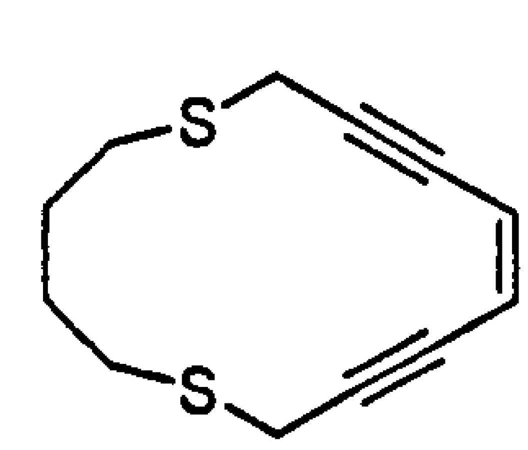

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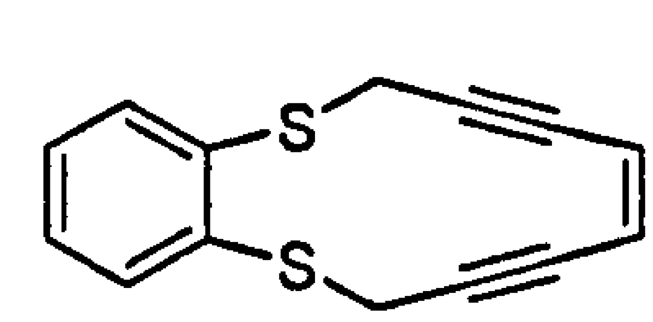


L

To my parents, inexhaustible friends.

Ai miei genitori, inesauribili amici.

Foreword

This thesis comprises three chapters that have been treated as separate entities. This is due to the fact that the background and the scientific objectives differ in each of them. Therefore the experimental sections and the bibliographies have been laid down separately at the end of each chapter. Also, molecule numbering is not progressive throughout the thesis but has been elapsed at the beginning of each chapter. Consequently, some molecules may appear in different chapters with different numbering.

AKNOWLEDGMENTS

In a hectic and ever-moving city like London, three years is a rather long period. A lot of thing can happen and one certainly ends up meeting a lot of people. With some of them one spends quality time, others are meteorites who quickly disappear from the horizon.
After having left the craze almost two years ago, my memories start now to blur. Nevertheless I can tell you that the after-taste is extremely pleasant, although I do not remember every single item who happened to be on my menu. I learned a lot, I had a great time, I made friends. I cannot thing of any three better things. I would not know how to describe myself if not as an extremely lucky chap.
I guess you want the names…I would like to thank, first and above all, my supervisor: Richard "*The Governor*" Grainger. Without the energy derived from his passion, patience and full commitment I would have never got there (where?). I really hope he would feel that after these three years he has earned himself a fellow chemist but most importantly a friend. Then, well down the line, there is the bunch of looser I had the disgrace to share my endless lab hours with: "scumbag" Patel, "Pree!", Wallywally, Patszy and Paolo. Thank you guys for developing with me that invaluable tool known as the "Schlenk Column". A special thank to my first labmate, Alex, who immensely enriched my vocabulary of filthy Greek expressions. All the lads and gals from the Chemistry department at King's. I will never be grateful enough for sharing with me the pains of the Refectory *cuisine:* Clara, Cristina, Donatella, Egizia, Emilie, Elisabbotta, Hubert, Jose, Meritxell, Paola, Rubina, Sebastien, Warwick and the "Spanish battalion". Also, for the formidable number of parties we crashed at: Aurora, Felipe, Juanito, Raul, Roger, Sophia and Yole and the some five zillion Catalans who are slowly taking over the city. A very, very, very special hug to the person who more than anybody else walked along with me through this unforgettable experience. Emanuel. Those moments in front of the "departmental pictures" board were thoroughly worth living. Your friendship will linger nicely in my heart. Surviving the city would have been a lot tougher without my hard-core friends: Adriana, Cesco, Elina, Gemma, Gen, Giora, Laura, Marco, Mischa, Moriella, Stefano, Venia and Virillo. You guys know how much you are worth to me and how much I love you. No words can really express it adequately. A word of gratitude to the LAGOT community at large. You are now my enlarged family, brother and sisters. It is relieving to know to have so many. Those animal parties in Beckon won't be easily forgotten….A special mention to those three who made my settling down in Bxl a lot easier and nicer: Benito, Pat and Guillermo.
Finally, allow me to switch to my own language. Grazie infinite mamma e papa'. Grazie infinite. Se sono quello che sono (e di cui spero andiate fieri) lo devo principalmente a voi. Se solo potessi ritornarvi una piccola parte della bonta' che continuamente riversate sopra di me.
Infine Cristina, la mia gold...woman, un plauso a nome del WWF per aver avuto il buon cuore di raccattare un goldfish randagio.

TABLE OF CONTENTS

List of Abbreviations

Ar:	Aromatic.
1,4-CHD:	1,4-Cyclohexadiene.
m-CPBA:	meta-Chloroperbenzoic acid.
DCM:	Dichloromethane.
DFT:	Density Function Theory.
DMF:	N,N-Dimethylformamide.
DMSO:	Dimethyl sulfoxide.
DSC:	Differential Scanning Calorimetry.
HREI:	High resolution Electron Impact.
IMS:	Industrial Methylated Spirits.
LAH:	Lithium Aluminium Hydride.
LREI:	Low Resolution Electron Impact.
NMR:	Nuclear Magnetic Resonance.
OT:	Onset Temperature.
TEMPO:	2,2,6,6-Tetramethyl-1-piperydinyloxy, free radical.
THF:	Tetrahydrofuran.
THP:	Tetrahydropyran.
TLC:	Thin Layer Chromatography.
TMEDA:	N,N,N', N' Tetramethylethylenediamine.

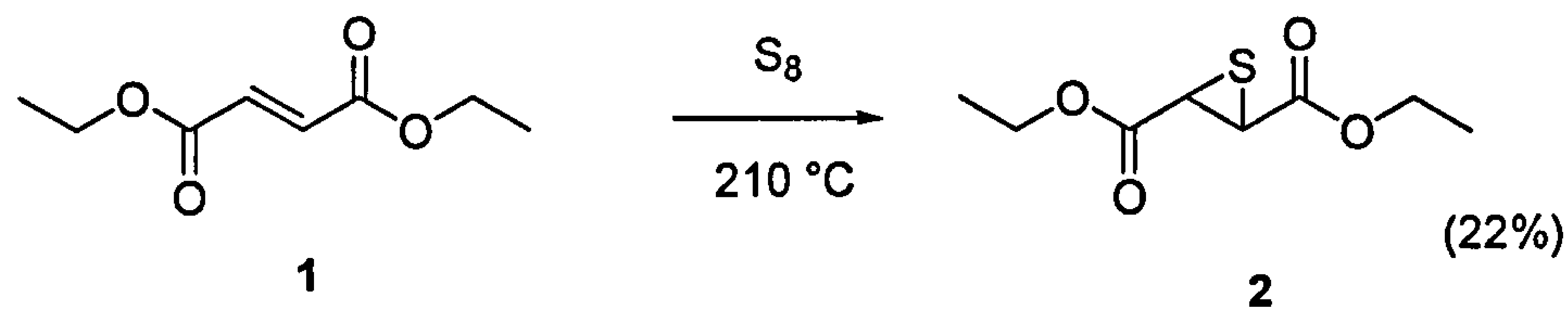
CHAPTER I:

Direct Thioepoxidation of Alkenes

BACKGROUND AND SIGNIFICANCE

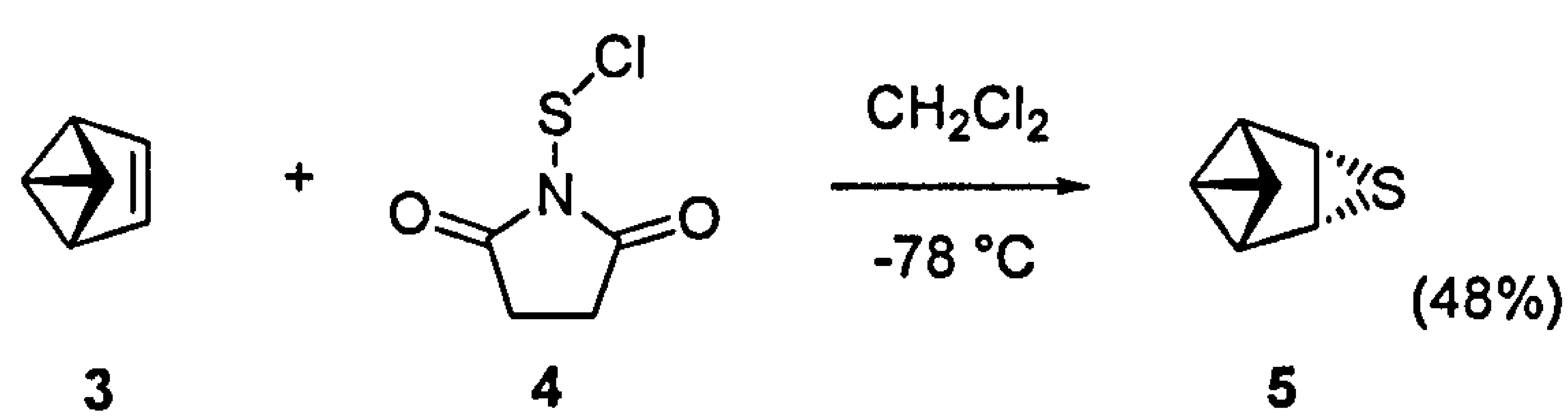
1.1.1. Episulfides from Alkenes.

There are few methods to convert alkenes directly to episulfides.[1] The first successful method reported dates back to the end of the 19th century, when (E)-fumaric acid diethyl ester **1** was converted to epithio-succinic acid diethyl ester **2** (Scheme 1.1).[1a]



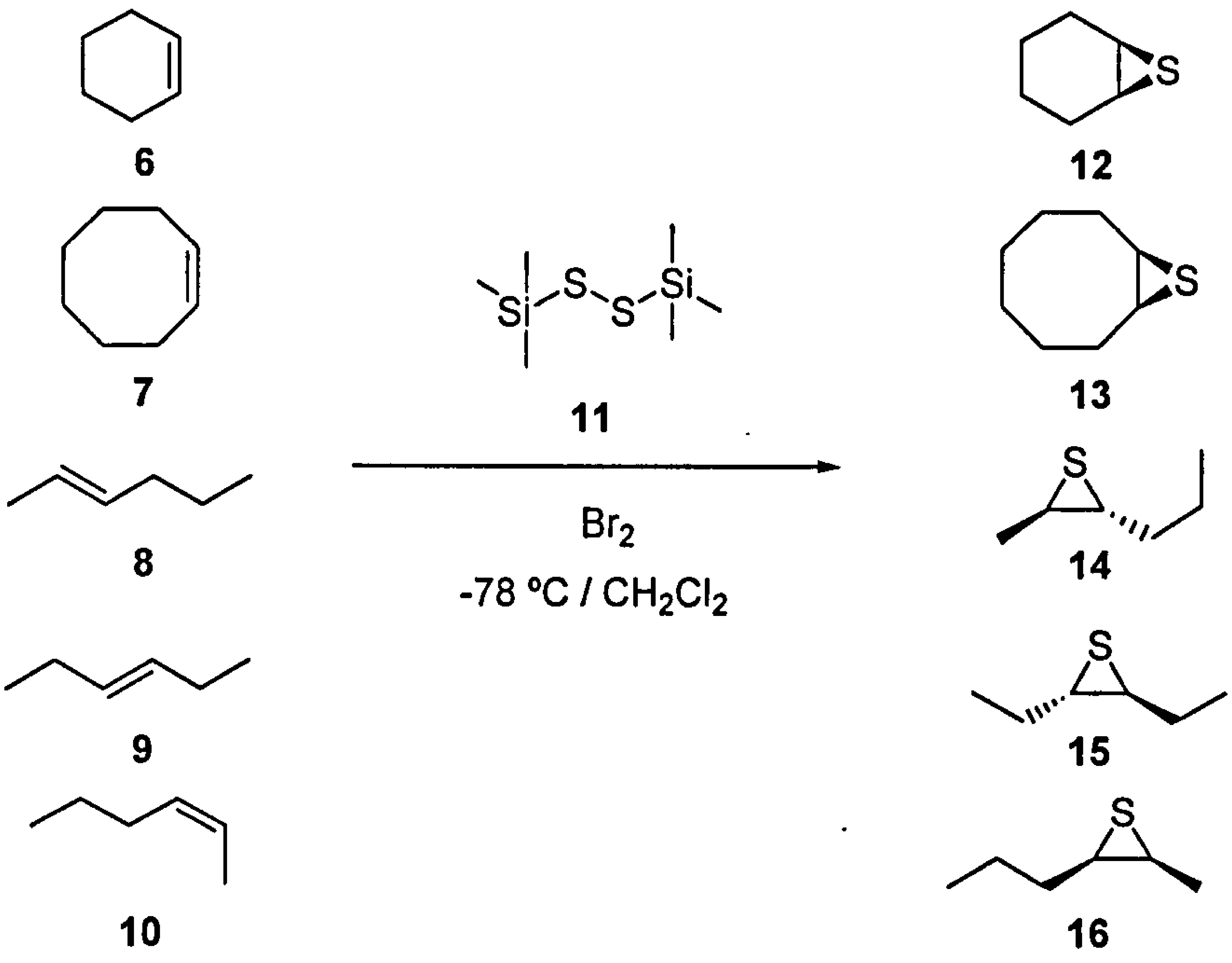
Scheme 1.1

It took almost a century before an alternative reagent was employed to carry out the same type of transformation;[1c] benzvalene episulfide **5** was synthesized from tricyclo[3.1.0.0^{2,6}]hex-3-ene **3** using succinimid-N-sulfenylchloride **4** (Scheme 1.2).



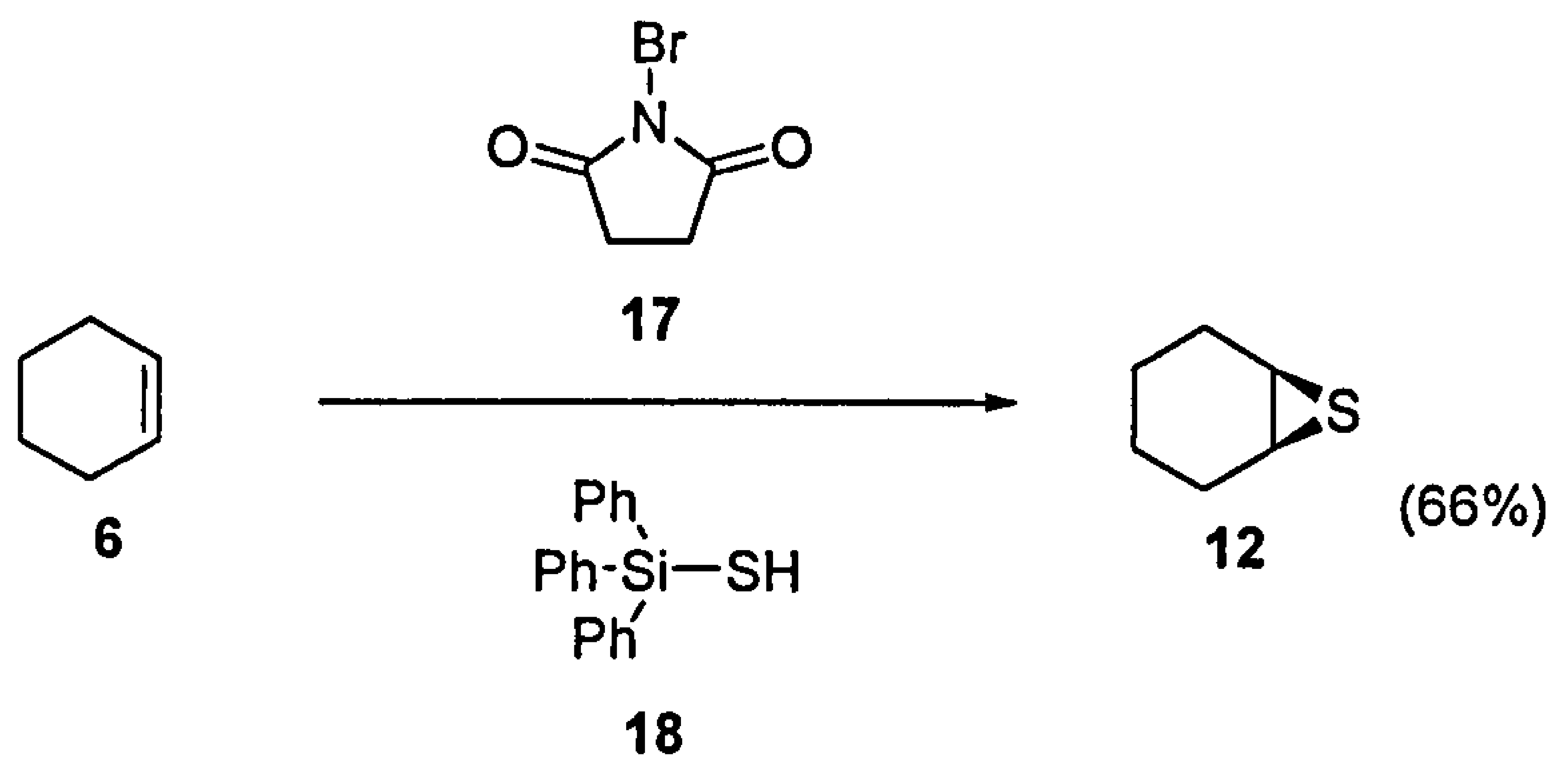
Scheme 1.2

Later, Capozzi and co-workers introduced bis(trimethylsilyl)sulphide **11** in the presence of bromine as a more widely applicable reagent.[1b] These conditions proved to be effective with a series of substrates, both cyclic and acyclic (Scheme 1.3).



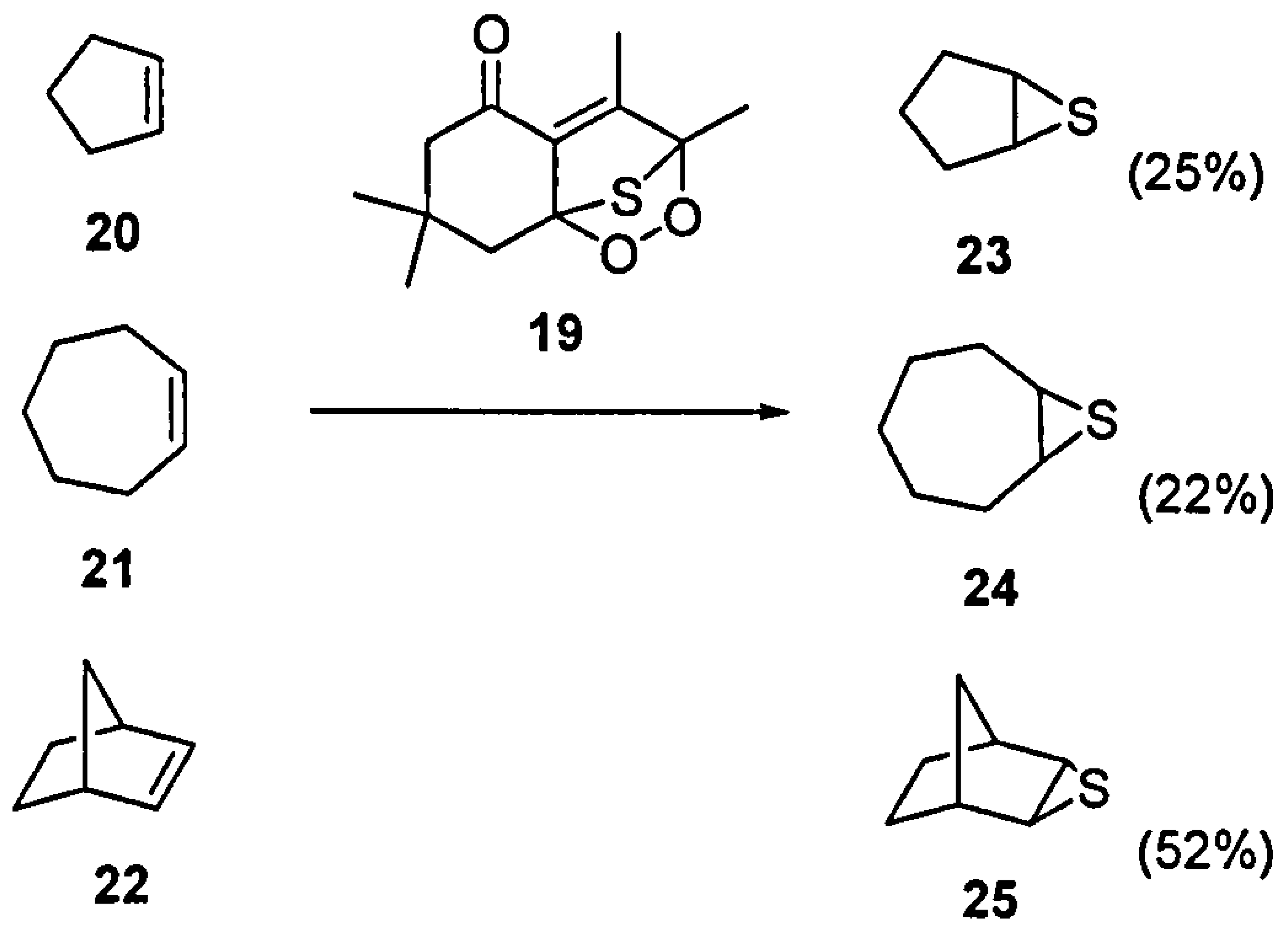
Scheme 1.3

The preparation of **12** was also achieved using N-bromosuccinimide **17** and triphenylsilanethiol **18** in benzene (Scheme 1.4).[1d]



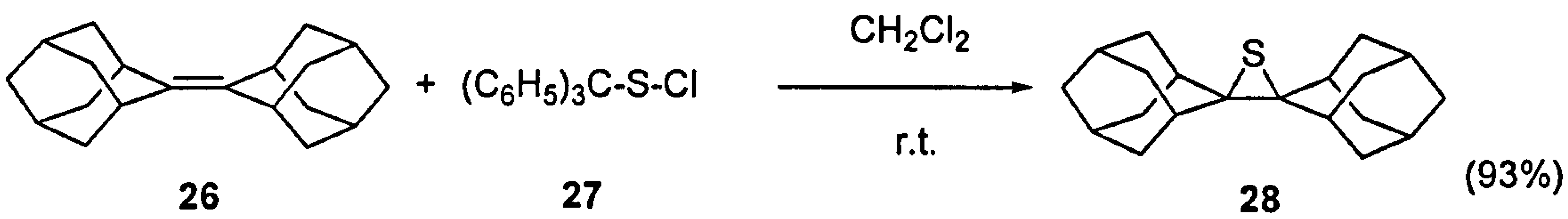
Scheme 1.4

Adam introduced another reagent that reacted with a rather wide series of substrates.[1e] Use of 3,3,7,8-tetramethyl-9,10-dioxa-11-thiatricyclo[6.2.1.0^{1,6}]undec-6-en-5-one **19** in $CDCl_3$ at room temperature permitted quite rapid transformation of compounds **6** and **7** to **12** and **13** respectively, although in low yield (5 and 31%). Nevertheless, other useful episulfides could be prepared directly (Scheme 1.5).



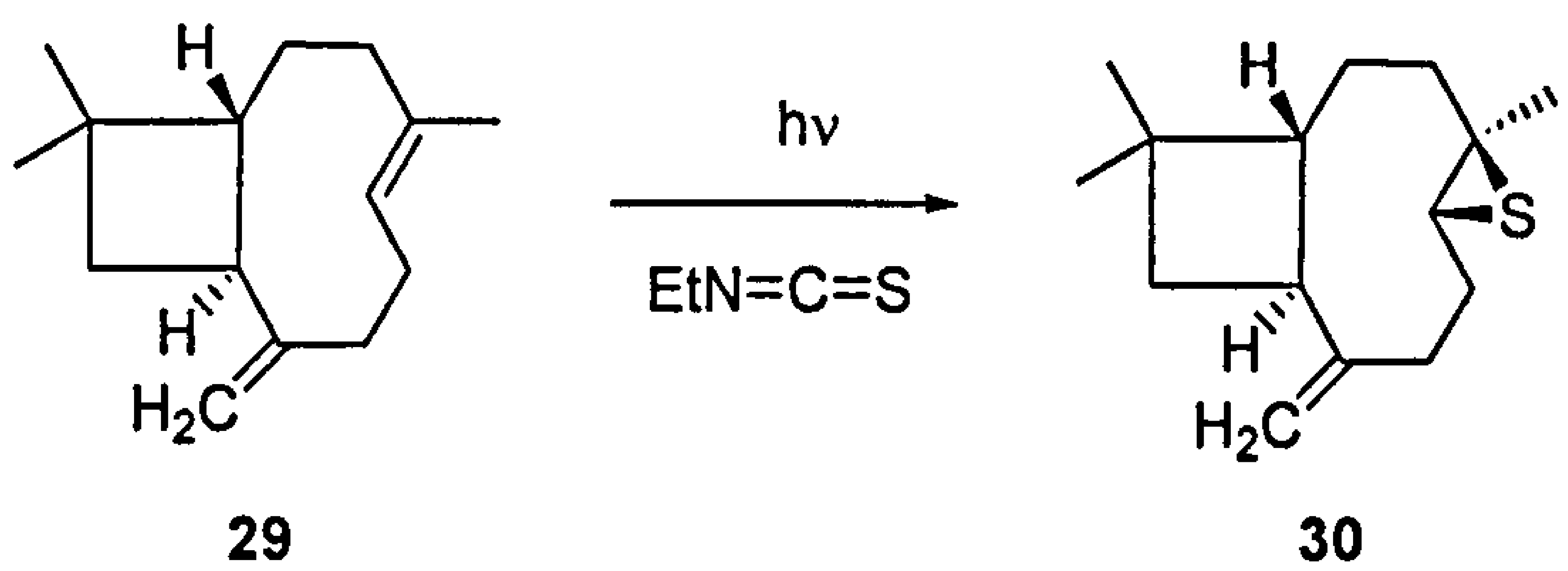
Scheme 1.5

Formation of biadamantylidene thiirane **28** from [2,2']biadamantanylidene **26** has attracted considerable attention. There are three independent reports of such a transformation, using SCl_2,[1i] elemental sulfur,[1l] and triphenylmethanesulfenyl chloride **27**.[1m] Use of the latter reagent improved the yield from poor to excellent (Scheme 1.6).



Scheme 1.6

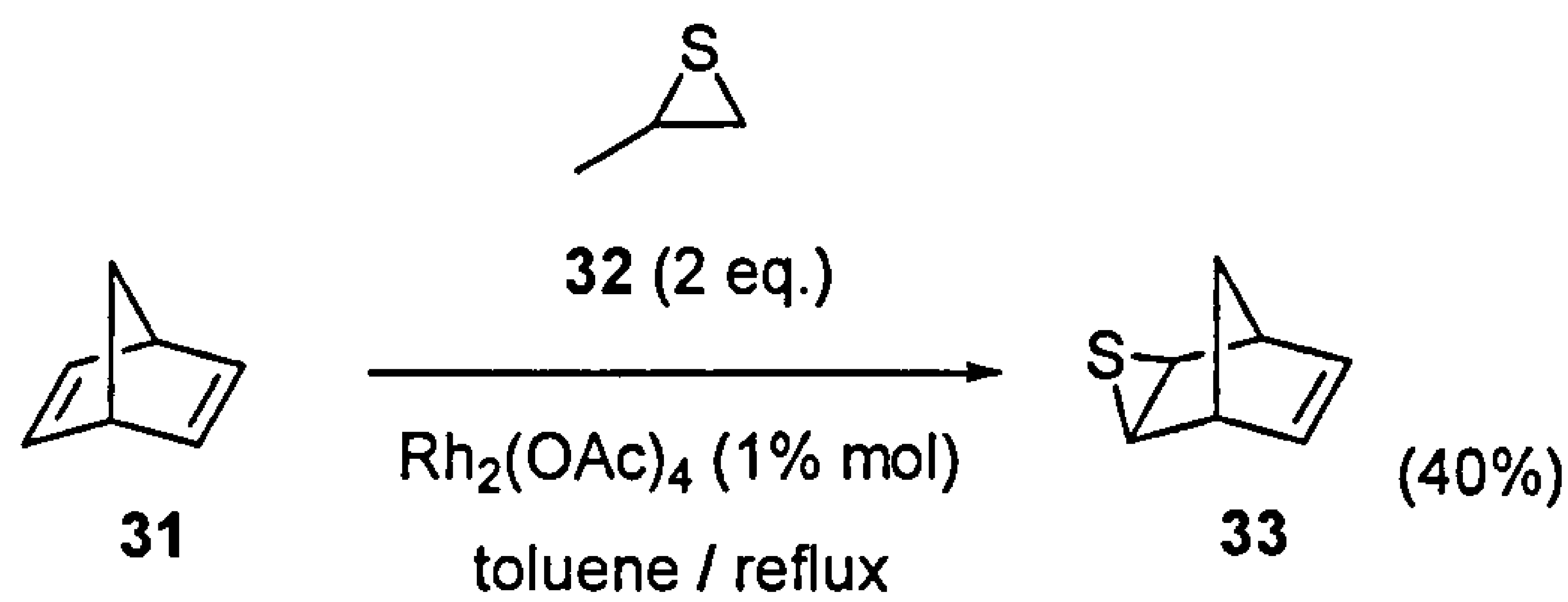
Other methodologies have been employed for direct thioepoxidation, although reports are confined to very specific substrates. Photochemical conditions, for instance, have permitted the preparation of 4-epithiocaryophyllene **30** using ethyl isothiocyanate as a source of sulfur, albeit after 4 days reaction in benzene (Scheme 1.7).[1h]



Scheme 1.7

Moreover **13** and **25** could be synthesised in very low yield upon irradiation of **7** and **22**, respectively, in the presence of a series of diaryl sulfines.[1a] Better yields were achieved with *trans*-**7** rather than *cis*-**7**.

Metal catalysis has also been employed for the synthesis of episulfides. Rhodium acetate catalyses the transfer of sulfur from propylene episulfide **32** to norborn-2-ene **22** and norborna-2,5-diene **31** to yield **25** (39%) and **33**, respectively (Scheme 1.8).[1f] Non-strained alkenes failed to react however.

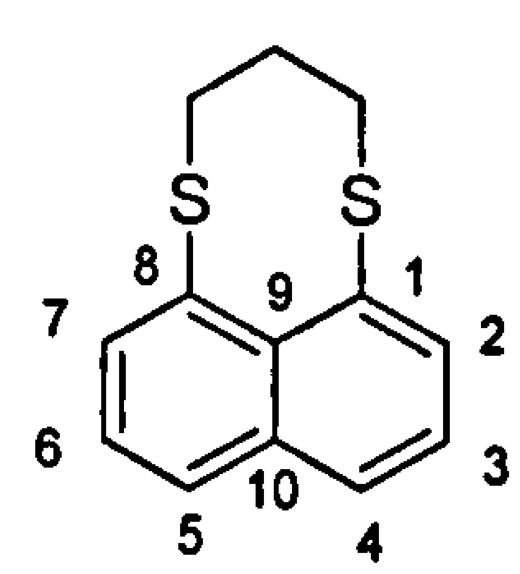


31 **33**

Scheme 1.8

1.1.2. *peri-peri* Transannular Interactions.

We envisaged that exploitation of transannular interactions in 1,8-disubstituted naphthalene systems represents an original starting point in the design of a new molecule capable of carrying out the direct thioepoxidation of alkenes. This assumption stemmed from the fact that it had been reported that chalcogen atoms appropriately arranged in space tend to repel each other.[2] Molecule **34** in Figure 1.1 exemplifies this type of interaction.



34

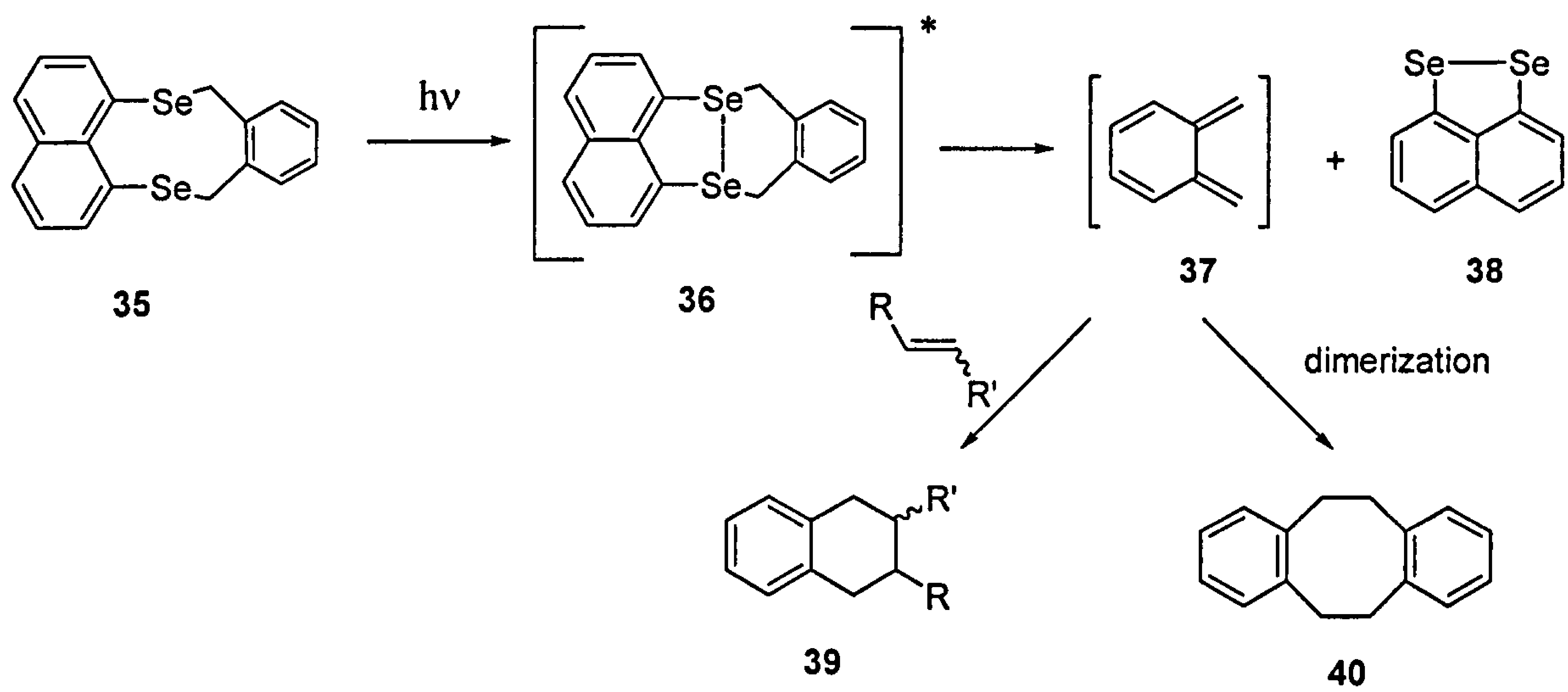
Figure 1.1

Conformational analysis on naphtho[1,8-b,c]-1,5-dithiocin **34** showed it to have a high level of constrain.[3] Owing to the geometry and rigidity of the naphthalene ring, the sulfur atoms, which are in the so-called "peri" positions,[4] are very close one to another and the p-type lone pair orbitals on sulfur are directed towards each other. As a result these fused systems suffer from a distortion in the planarity of the aromatic rings, which is detected normally along the C9-C10 axis.

In such a molecule the non-bonded S-S distance is 3.227 Å, shorter than twice the van der

Waals radius of sulfur (3.70 Å).[3] Under such conditions there is a strong driving force for the formation of a chalcogen-chalcogen bond.[5] This phenomenon has been exploited for synthetic purposes under photochemical conditions.[6]

One such example is the photochemically-induced decomposition of 8,13-dihydrobenzo[*g*]naphtho[1,8-*bc*][1,5]diselenonin **35** to give *o*-quinodimethane dimer **40** and naphtho[1,8-*cd*]-1,2-diselenole **38** (Scheme 1.9).[7]



Scheme 1.9

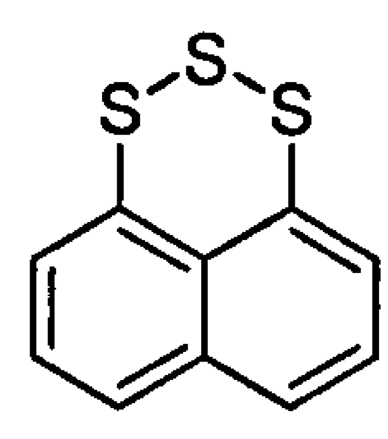
This reaction probably involves *o*-quinodimethane **37** as a transient intermediate after the formation of the photoexcited diselena dication **36** by photoinduced activation. The formation of **37** was identified by trapping experiments in the presence of olefins under UV irradiation. This reaction gave 100% recovery of **38**.

The photolysis of 8,13-dihydrobenzo[*g*]naphtho[1,8-*bc*][1,5]dithionin (the sulfur analogue of **35**) gave almost the same results as the selenium derivative.[8]

AIMS AND OBJECTIVES

1.2.1. The Design of a Novel Trisulfide.

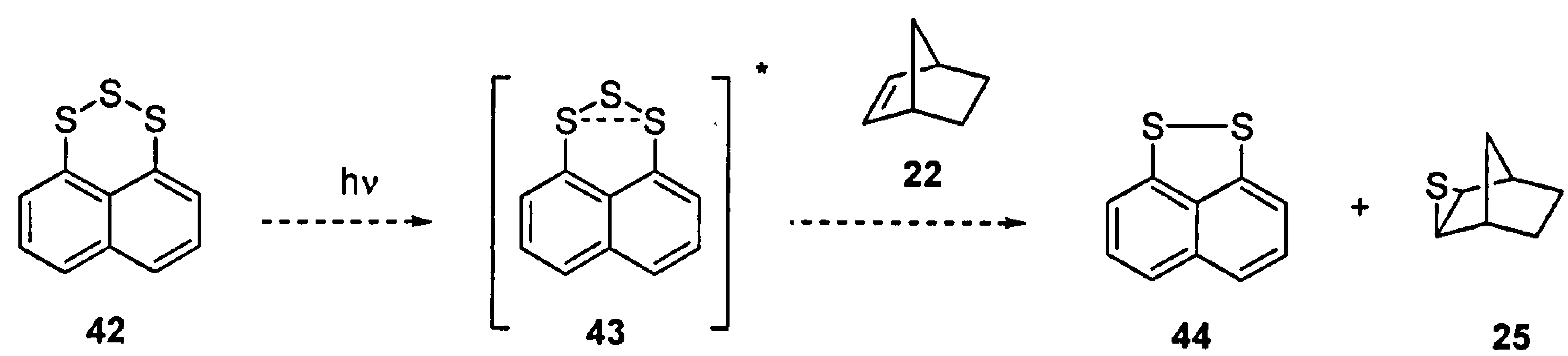
The precedents set out in the preceding section prompted us to pursue the synthesis of the novel trisulfide **42** (Figure 1.2).[9]



42

Figure 1.2

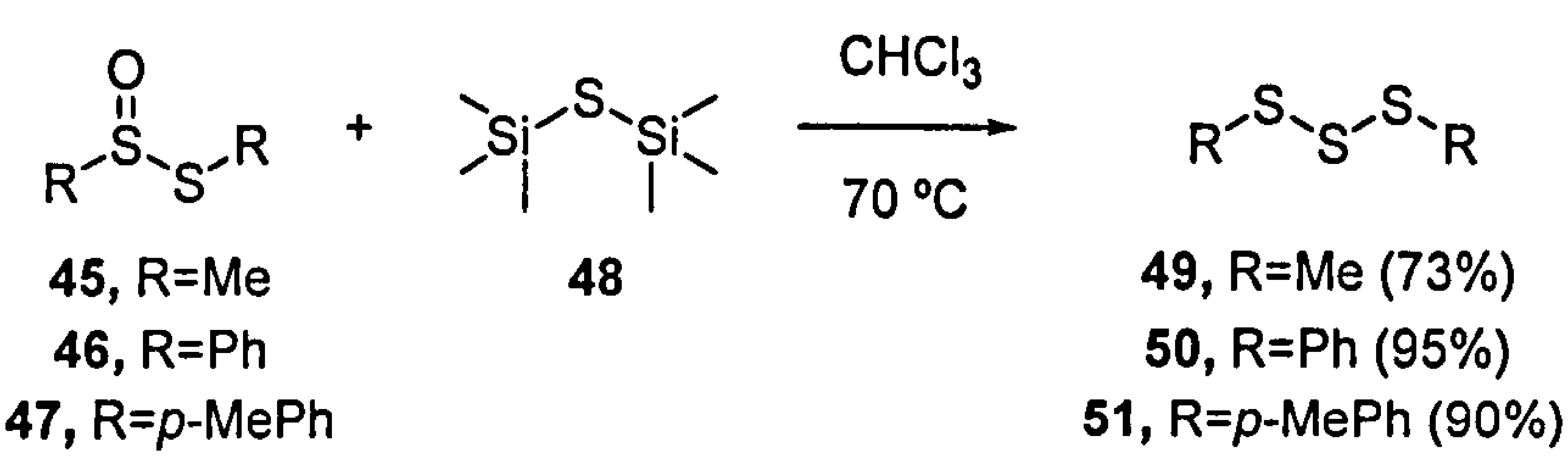
We anticipated that treatment of **42** under photochemical conditions would also promote the formation of a photoexcited dithio species **43**, capable in turn of delivering "S" to strained alkenes (Scheme 1.10).



Scheme 1.10

Disulfide [1,8-*c,d*]-1,2-dithiole **44** is the decomposition product which we would ideally recycle. We therefore designed the retrosynthetic analysis of **42** based on **44**.

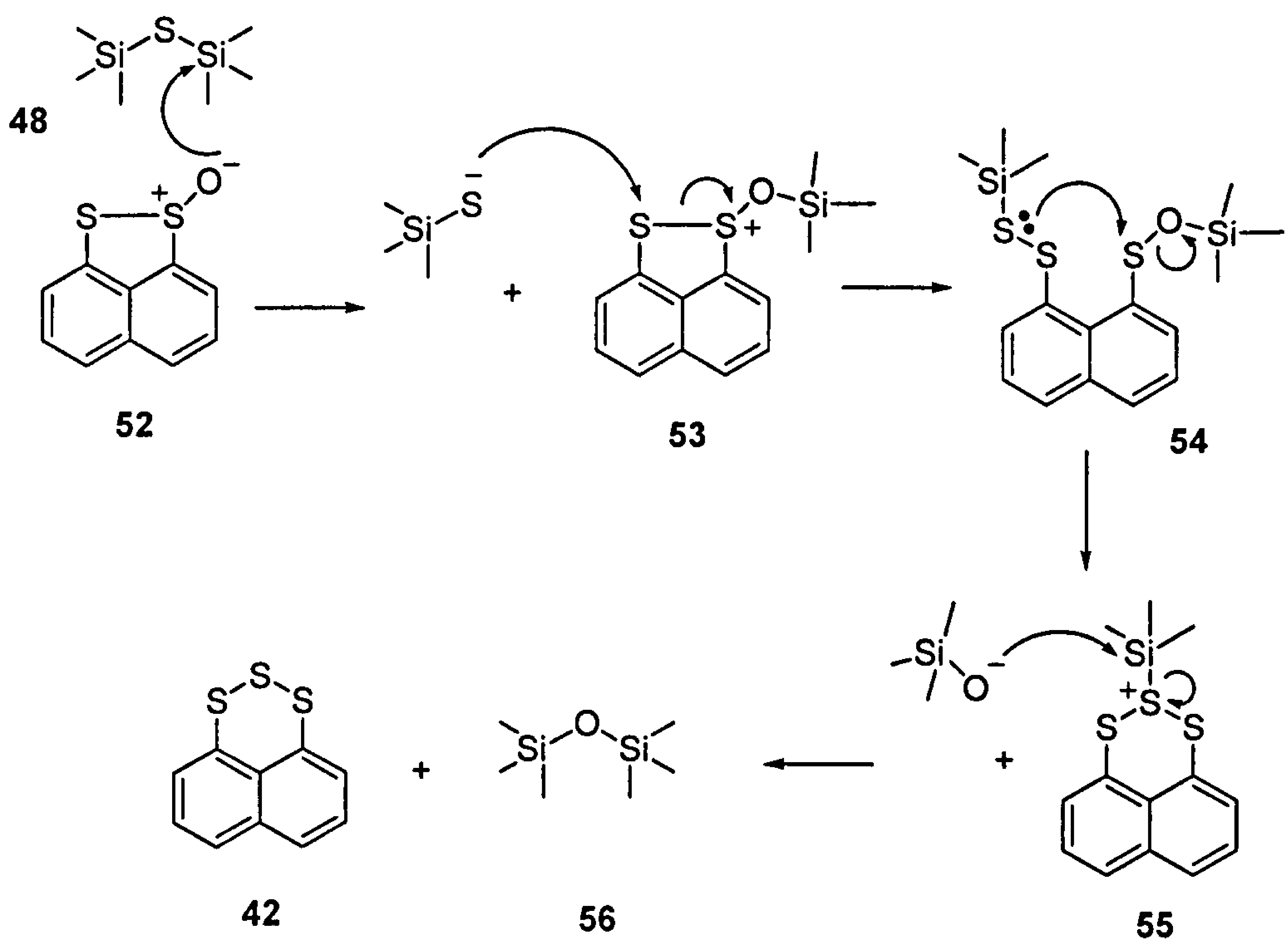
The reaction of hexamethyl disilathiane (TMS-S-TMS) **48** with thiosulfinates represents a possible approach to the synthesis of **42**. Capozzi and co-workers first reported the reactions shown in Scheme 1.11 for the generation of trisulfides.[10]



Scheme 1.11

Later other workers confirmed the methodology to work on other thiosulfinate esters, although the yields were somewhat lower.[11] The reaction is also known to proceed starting from thiosulfonates.[10b,12]

In light of such precedent, we foresaw that thiosulfinate **52** would react in the same manner with TMS-S-TMS **48** to afford trisulfide **42**. The proposed mechanism of reaction is depicted in Scheme 1.12.



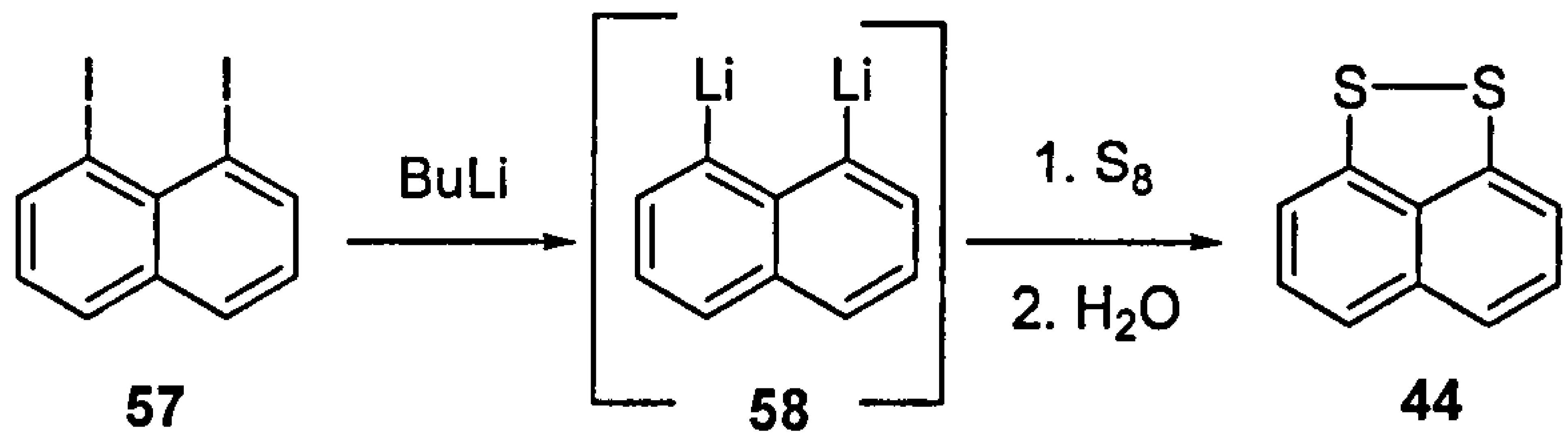
Scheme 1.12

Knowing that oxidation of **44** to **52** was a reported transformation,[13] the first task we faced was the synthesis of [1,8-*c*,*d*]-1,2-dithiole **44**.

RESULTS AND DISCUSSION

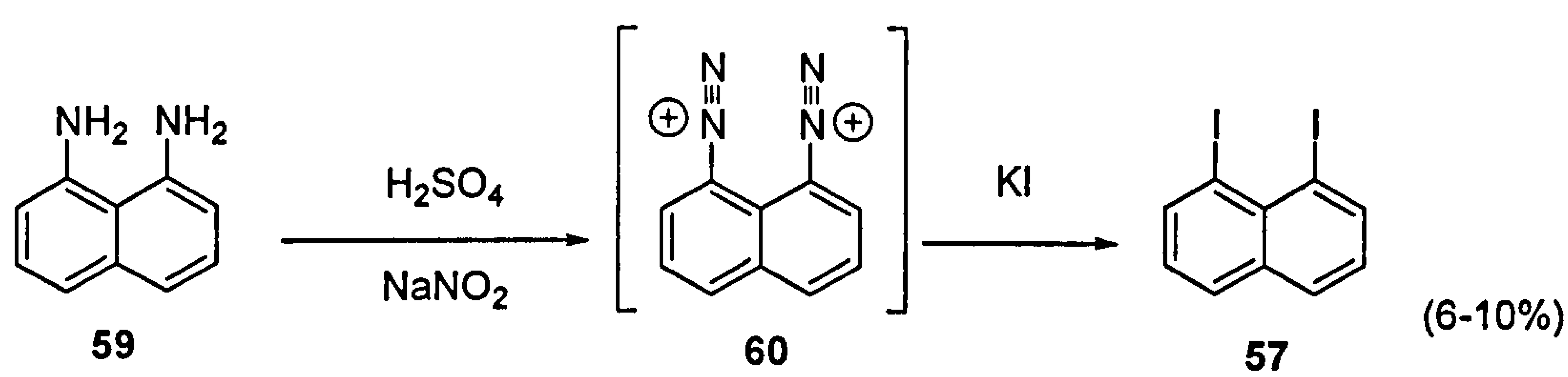
1.3.1. Synthesis of [1,8-*c*,*d*]-1,2-Dithiole.

There are several possible routes to the synthesis of **44**. A lithium-halogen exchange reaction on 1,8-diiodonaphthalene **57**, followed by quenching with electrophilic sulfur, seemed most attractive and it was therefore the subject of our initial approach (Scheme 1.13).[14] Intermediate **58** has been extensively utilised for the preparation of organic[15] and organometallic[16] 1,8-disubstututed naphthalenes.



Scheme 1.13

Accordingly, commercially available 1,8-diaminonaphthalene **59** was first converted into 1,8-diiodonaphthalene **57** via double diazonium salt **60** formation and subsequently treated with an aqueous solution of potassium iodide (Scheme 1.14).[17]

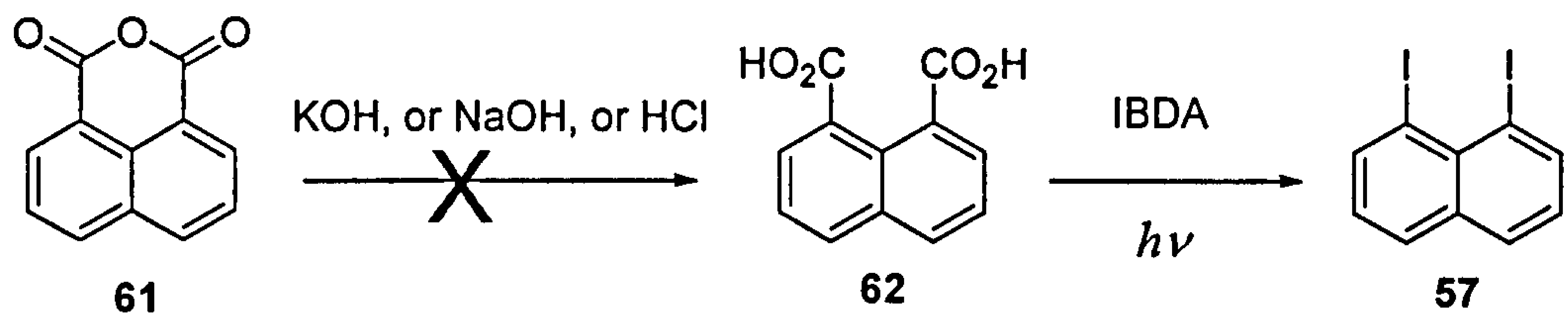


Scheme 1.14

This step proved problematic because of the considerable foaming that occurred upon heating, prior to the addition of potassium iodide. Several attempts were made to overcome this: purification of the starting material, increasing the size of the flask and the use of an overhead stirrer. Overall, the yields were never satisfactory or close to those reported. Other authors reported similar disappointing yields (10%) upon repetition of this procedure.[18] The reaction in Scheme 1.14 was also attempted using an acid with better solubilising properties, such as trifluoroacetic acid. No product at all was observed.

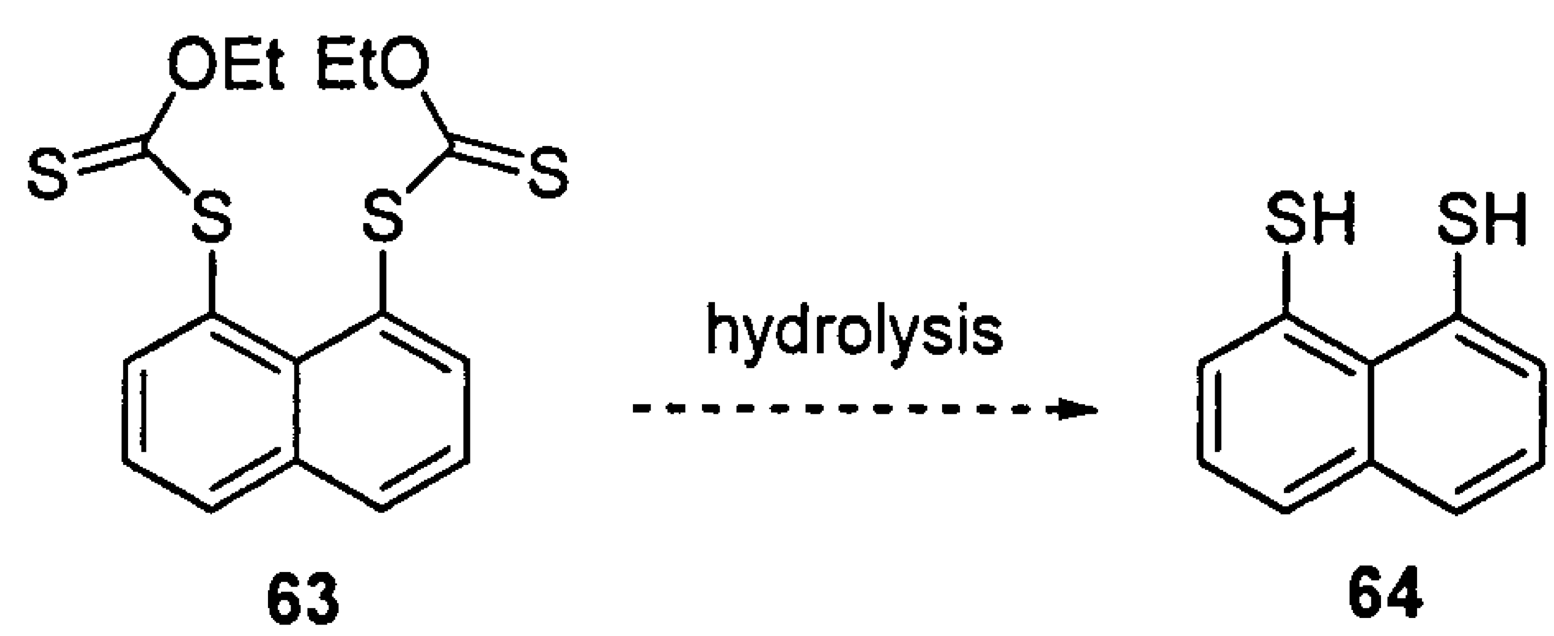
With small amounts of **57** in hand, lithium-halogen exchange and quenching with sulfur was carried out as reported in the literature (Scheme 1.13). However, difficulty in isolating the product in high enough purity led to the abandonment of this route.

An alternative synthesis[18] of **57** is based upon irradiation of dicarboxylic acid **62** in the presence of $PhI(OAc)_2$. At the time of the publication the starting material was commercially available, now it is no longer. Attempts to synthesise **62** by hydrolysis of the available naphthalene anhydride **61**, both in acid and basic conditions and in one or two-phase systems, led only to recovery of the starting material (Scheme 1.15).



Scheme 1.15

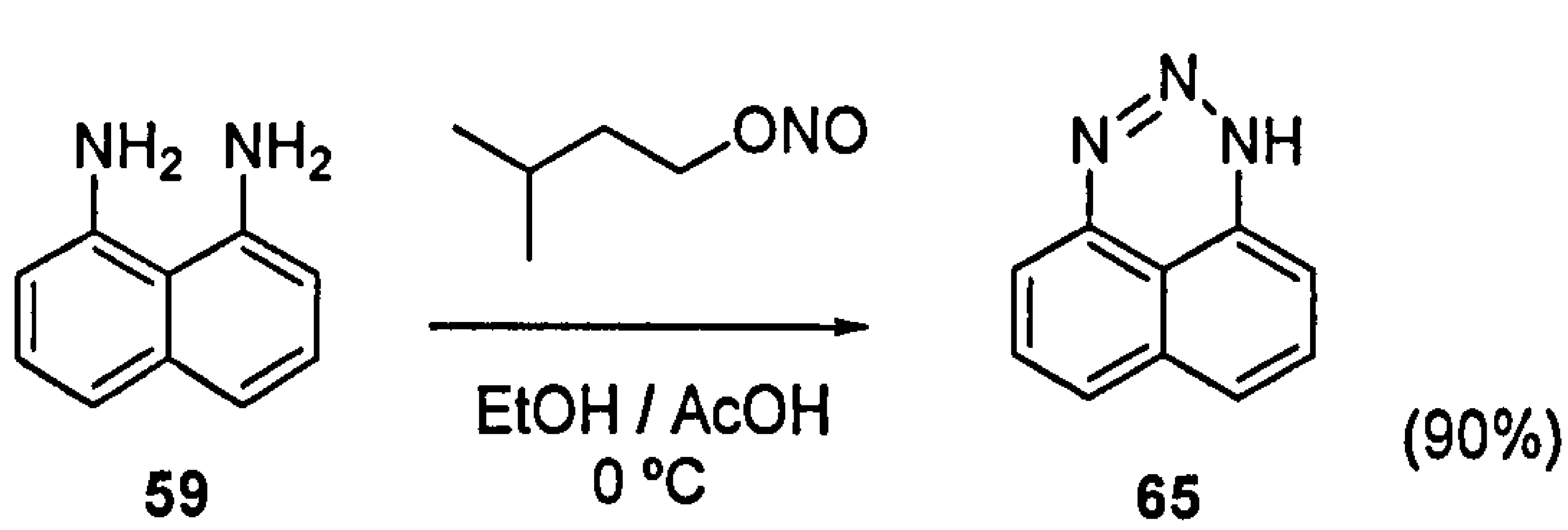
An alternative, but to date unexplored, way to obtain **64**, was through the hydrolysis of naphthalene-1,8-dixanthate **63** (Scheme 1.16), modifying a procedure already in the literature.[19]



Scheme 1.16

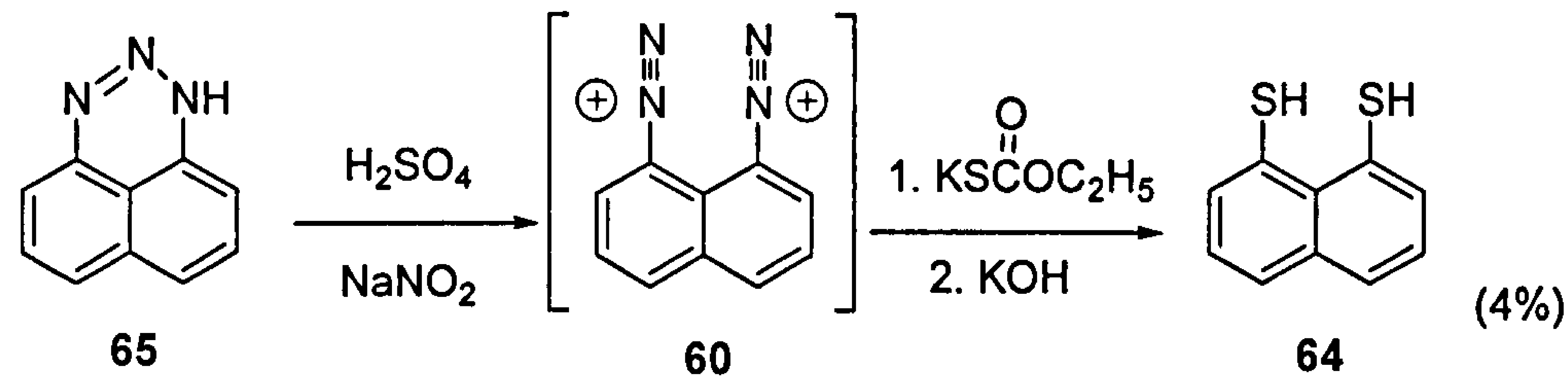
This is a procedure frequently used to make monoaryl thiols. Thiocresols, for instance, are prepared by alkaline hydrolysis of tolyl ethyl xanthates, obtained from toluenediazonium chloride and potassium ethyl xanthate.[20]

To this end, naphthalene triazine **65** was first prepared, in very good yield, as a convenient precursor to the bis-diazonium salt **60** (Scheme 1.17).[21]



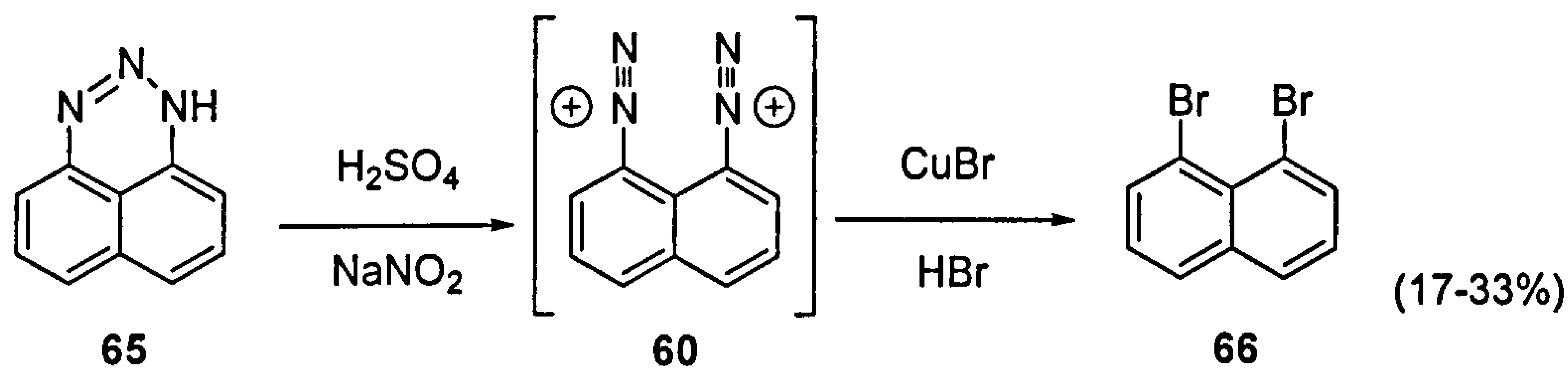
Scheme 1.17

Nevertheless, several attempts to convert **65** directly into **64** gave extremely poor yields (Scheme 1.18).



Scheme 1.18

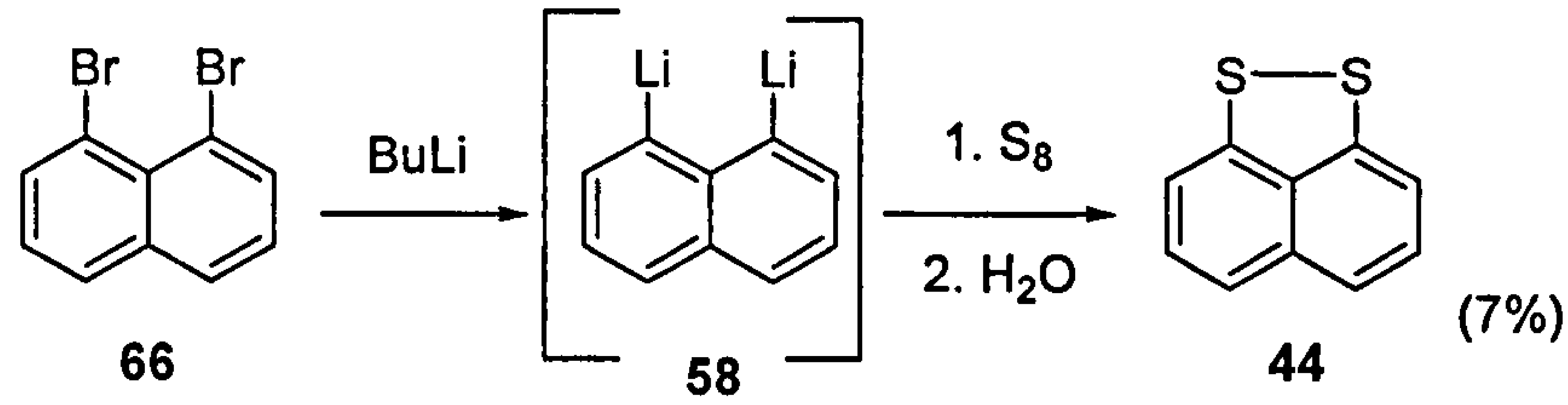
A step-by-step analysis suggested that the bottleneck for the reaction was the formation of the bis xanthate **63**, which could never be detected. Similar attempts to obtain the xanthate **63** directly from **59** via **60** also met with failure. Finally, it was possible to convert triazine **65** into 1,8-dibromonaphthalene **66** in acceptable yield (Scheme 1.19).[22]



Scheme 1.19

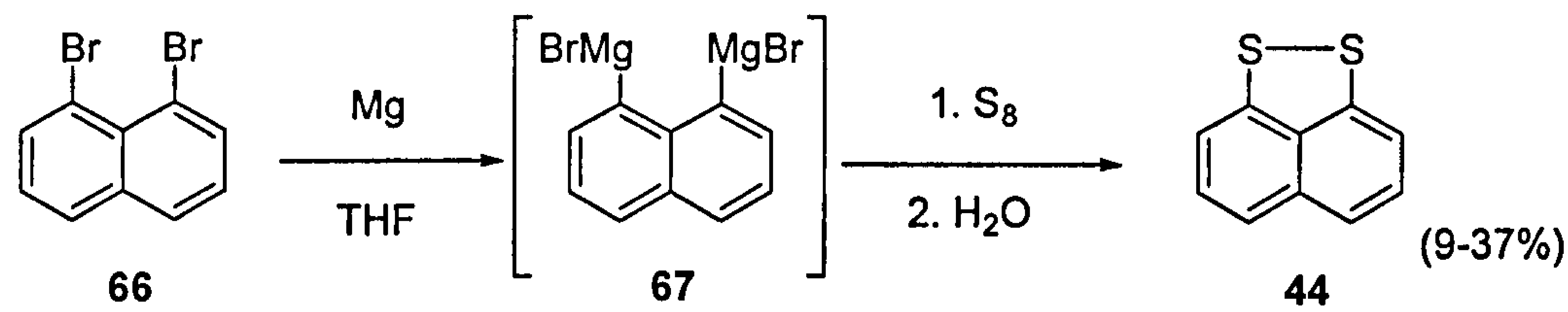
This reaction was carried out a number of times, varying the conditions (such as temperature, rate of addition and reaction time). The best yields were observed in conjunction with the slow addition of sodium nitrite. Compared to the reaction described in Scheme 1.14, the mixture did not foam to such an extent. Moreover, dibromide **66** can be isolated pure as a white crystalline solid after column chromatography. Again, the replacement of sulfuric acid with trifluoroacetic acid resulted in complete failure.

As for **57**, lithium-halogen exchange of **66**, followed by quenching with elemental sulfur, gave **44** in poor yields (Scheme 1.20).



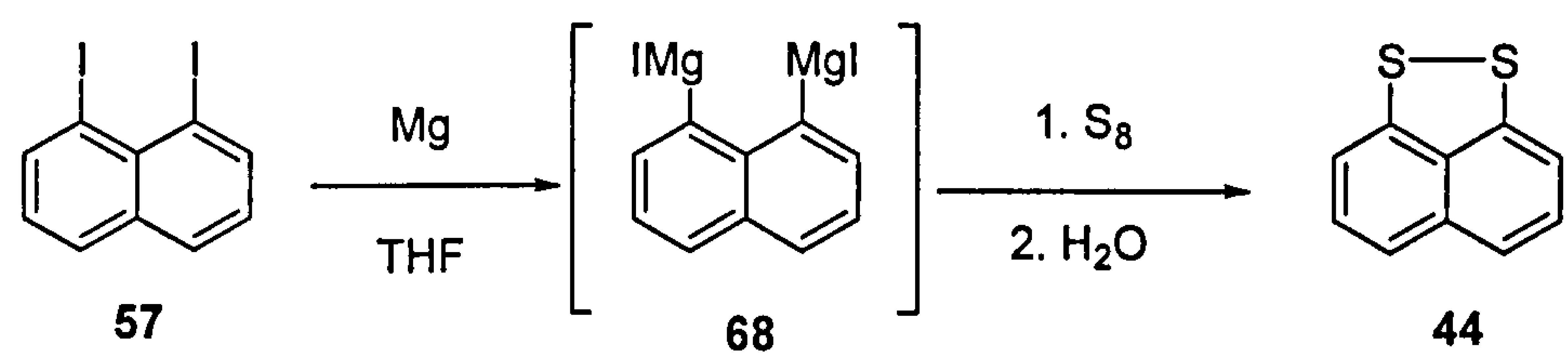
Scheme 1.20

However, a more successful method to favour attack on electrophilic sulfur was found through formation of a double Grignard **67** (Scheme 1.21).[23]



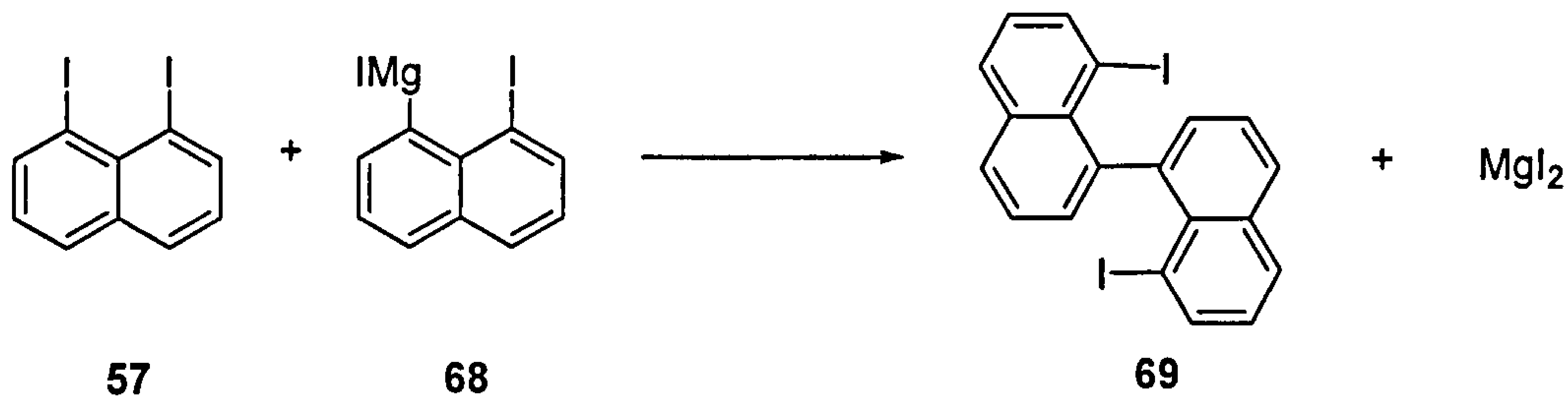
Scheme 1.21

Using this method, reasonable quantities of disulfide **44** can be prepared. The best yields were obtained through the addition of Grignard *via* cannula to a suspension of S_8 in THF at room temperature. Portionwise addition of S_8 to the Grignard gave inferior results (9-22%). A similar approach can be followed also starting from 1,8-diiodonaphthalene **57** (Scheme 1.22).



Scheme 1.22

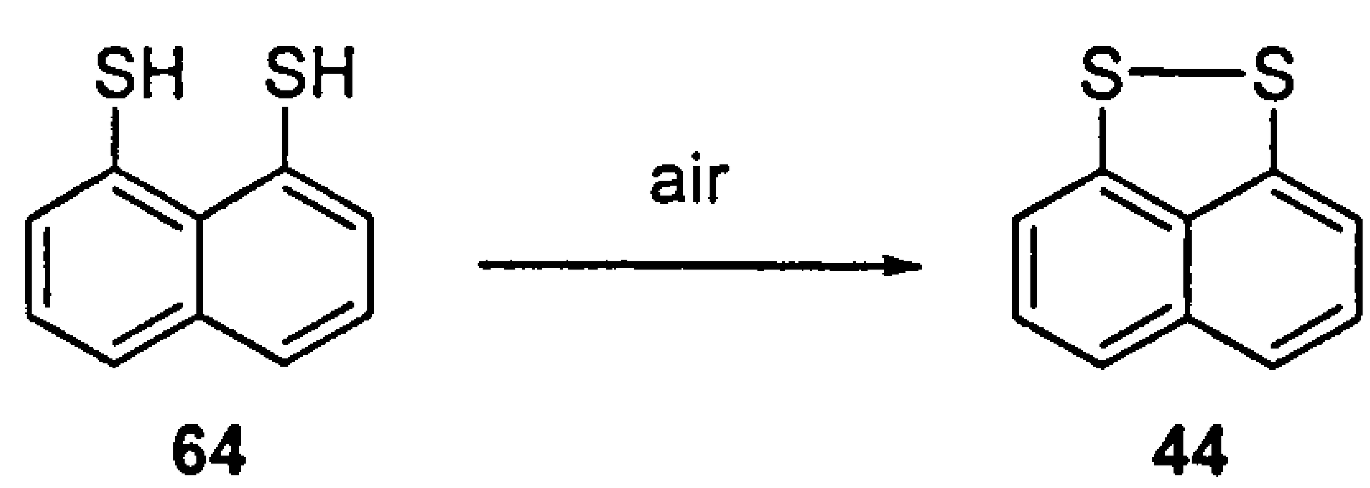
Substrate **57** was effectively prepared following the reaction in Scheme 1.19, where quenching of intermediate **60** with potassium iodide afforded the title compound in acceptable yields (15-32%). Two reactions were set up following Schemes 1.21 and 1.22; an equal number of moles of **57** and **66** were used under exactly the same conditions, only to prove the superiority of the dibromo-substituted naphthalene **66** over 1,8-diiodonaphthalene **57**. Substrate **57** seemed more prone to undergo formation of the magnesium dihalide, according to Schlenk equilibrium, possibly due to the lower solubility of MgI_2 in THF compared to that of $MgBr_2$. (Scheme 1.23).



Scheme 1.23

To minimize this problem, the use of 2-methyl tetrahydrofuran as a solvent has been proposed.[24] It was suggested that the higher solubility of MgI_2 in this solvent would result in a reduced loss of intermediate **68** due to the reaction in Scheme 1.23. In our case the employment of this stratagem did not lead to a substantial improvement. The yields were slightly better, but not enough to justify the use of so expensive a solvent.

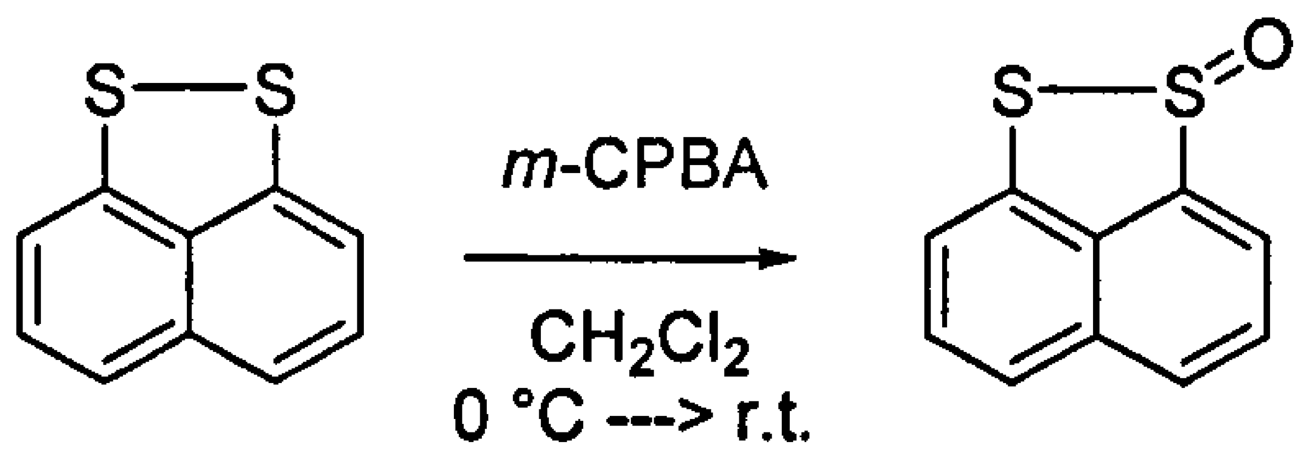
The protocol underlined in Schemes 1.17, 1.19 and 1.21, although lengthy, allowed us to prepare gram scale quantities of the target compound **44** using cheap reagents. A superior method of preparing compound **44** is described in Chapter 2. Noteworthy was the fact that the product we isolated after purification was always disulfide **44** and never dithiol **64**. There are two possible explanations: either that quenching **67** with sulfur afforded **44** directly or that **64** oxidises rapidly when exposed to air (Scheme 1.24).



Scheme 1.24

1.3.2. Synthesis of Thiosulfinate Naphtho(1,8-cd)-1,2-dithiole-1-oxide.

With **44** in hand we proceeded with its oxidation to thiosulfinate **52** (Scheme 1.25).



44 **52** (99%)

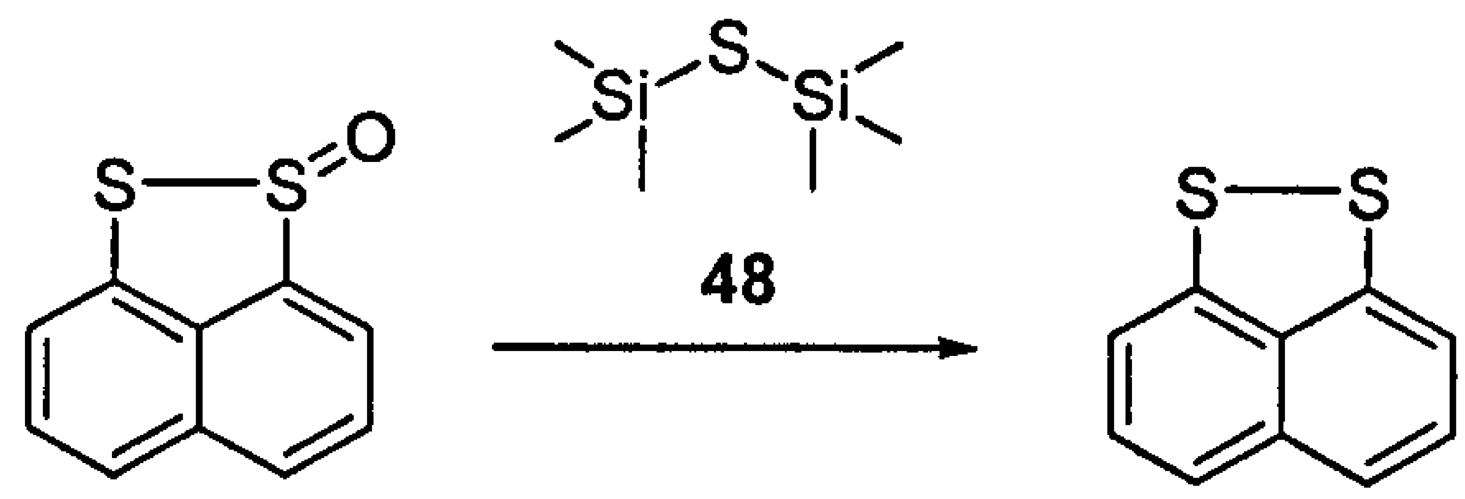
Scheme 1.25

There are three reported methods for the oxidation of disulfide **44** to thiosulfinate **52**. Among these we chose to use *m*-chloroperbenzoic acid (m-CPBA) due to its availability and superiority.[13a] In fact conversion of **44** to **52** was quantitative and yields were consistently higher then those reported in the literature.

1.3.3. Synthesis of Trisulfide 1,2,3-Trithia-phenalene.

We then tried to react thiosulfinate **52** with TMS-S-TMS **48** to form **42**. Adopting the conditions reported by Capozzi,[10b] we heated a mixture of **52** and **48** in chloroform to 60 °C. After 15 hours, **52** had substantially not reacted (TLC); nevertheless a faint spot due to a compound of lower polarity could be detected. We then decided to raise the temperature to reflux (72 °C). After reflux overnight, starting material was still present but the new spot was more visible, along with a further one. We interrupted the reaction and separated the components by column chromatography. Neither of them was of sufficient purity and quantity to provide useful information after ^1H NMR analysis. The use of a non-chlorinated, higher boiling solvent such as toluene gave no reaction at all after 19 hours at reflux.

Our attention turned to a higher boiling halogenated solvent, 1,2-dichloroethane (b.p. 83 °C). After 20 hours at reflux, the presence of unreacted thiosulfinate was revealed by TLC; unfortunately, purification of the reaction mixture only afforded disulfide **35** and elemental sulfur (Scheme 1.26).

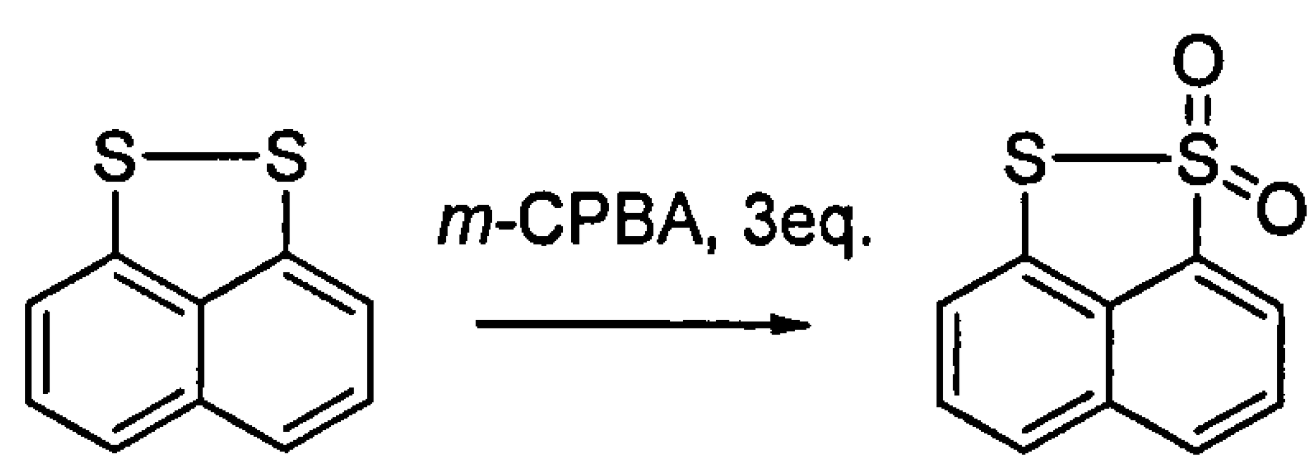


52 44

Scheme 1.26

The reaction was repeated and heating continued until total disappearance of starting material was observed, however the isolated products were the same. Although the result was unexpected, bibliographical research revealed that the reduction of thiosulfinates to disulfides by **48** has previously been reported.[15]

As mentioned before, trisulfides can be prepared using reagent **48** also starting from thiosulfonic acid S-esters. We therefore tried to oxidize disulfide **44** to thiosulfonate **70** using two equivalents of m-CPBA. Even in refluxing dichloromethane the reaction produced mostly thiosulfinate **52**. For the reaction to be driven further, an excess of oxidizing agent had to be used (Scheme 1.27).

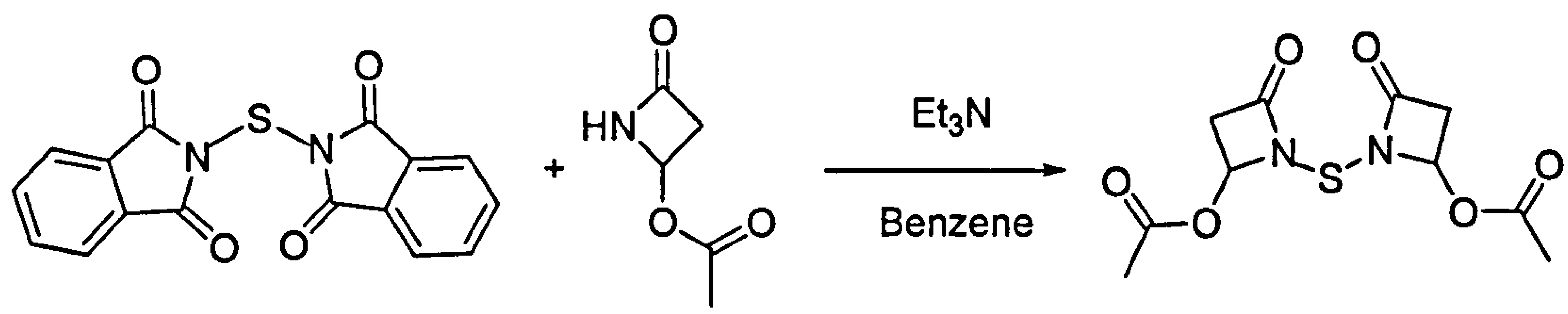


44 70

Scheme 1.27

Under these conditions a mixture of products was obtained; spectroscopic data confirmed the presence, among others, of the desired product. Yields, however, were unsatisfactory and separation unachievable.

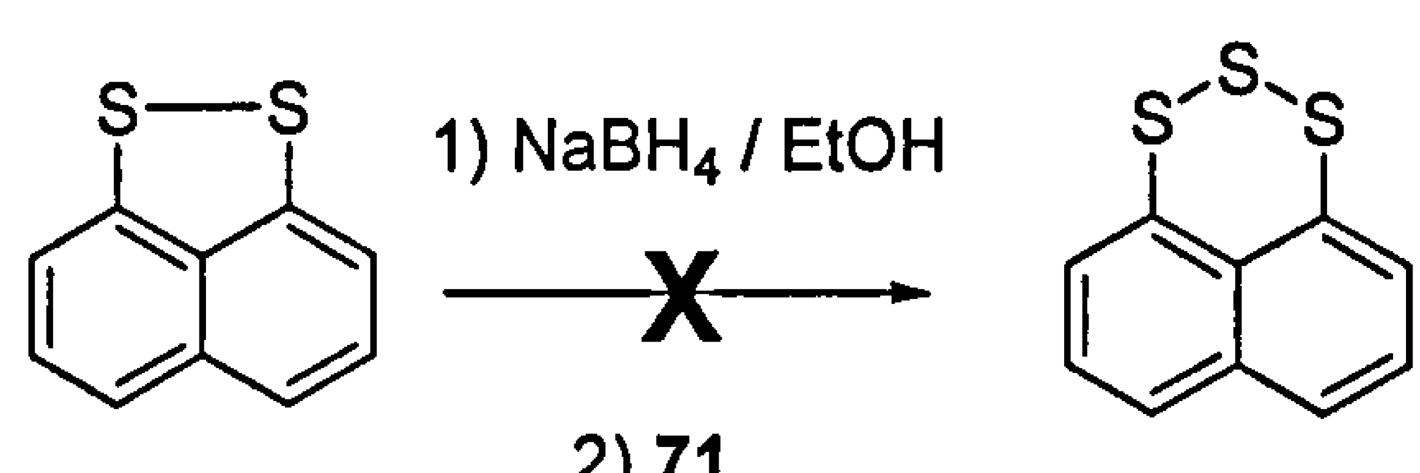
Since the reaction shown in Scheme 1.26 did not give the expected product, we considered an alternative approach to the synthesis of **42**. *N,N'*-Sulfanediyl-bis-phthalimide **71** is known to be susceptible to nucleophilic attack. The "leaving group" nature of the two phthalimide units permits the delivery of a sulfur atoms in acceptable yields, as underlined in the example below (Scheme 1.28).[25]



71 72 73

Scheme 1.28

Our hope was that a similar sulfur transfer would occur on treatment of dithiol **64** with *N,N'*-sulfanediyl-bis-phthalimide **71**. Accordingly, the reduction of disulfide **44** was carried out with an ethanolic suspension of $NaBH_4$.[26] Successful advancement of the reaction was testified by discolouration of the solution. Subsequent addition of **71** and stirring at room temperature only led to slow re-oxidation of **64** to **44**. Repetition of the reaction at higher temperature (60 °C) did not change the outcome (Scheme 1.29).

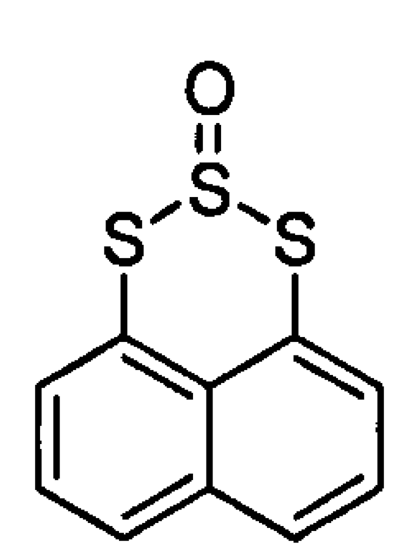


44 42

Scheme 1.29

Reaction in the presence of a base was also attempted. After $NaBH_4$ reduction and acidic work-up, the dithiol **64** was isolated. A mixture of **64** and pyridine was added dropwise to a solution of **71** in diethyl ether. Again, disulfide **44** was recovered quantitatively.

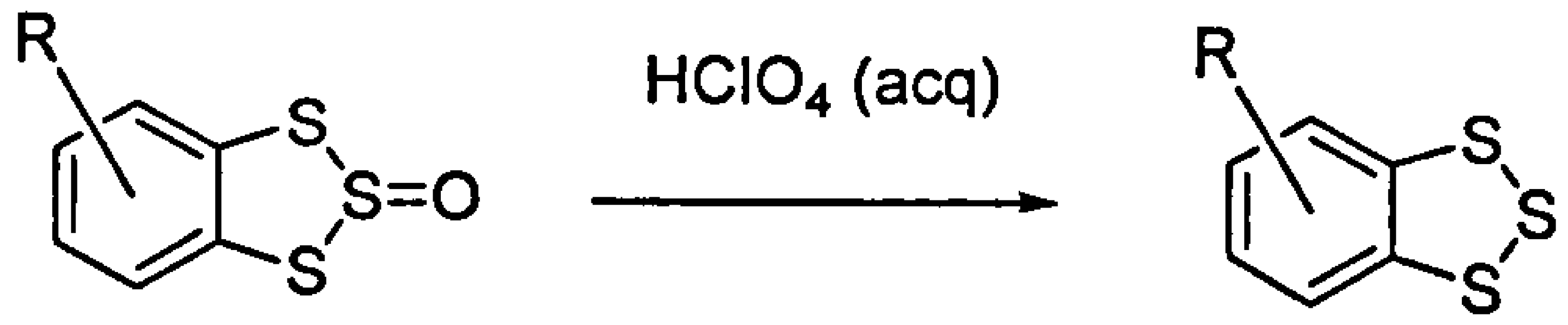
The successful synthesis of trisulfide oxide **74** (*vide infra,* Chapter 2) suggested an alternative route to trisulfide **42** (Figure 1.3).



74

Figure 1.3

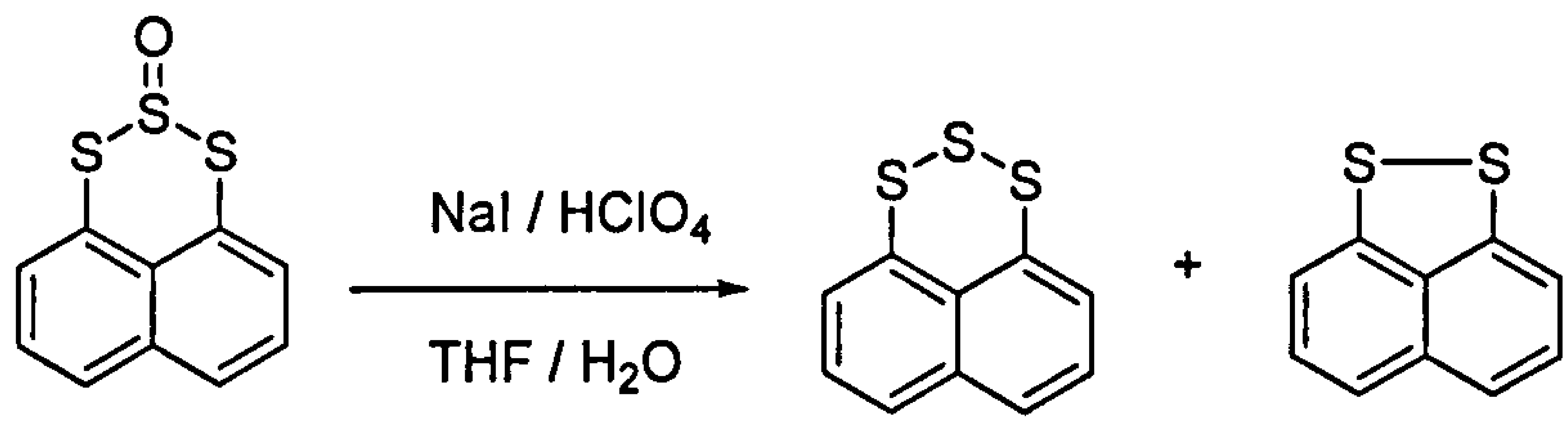
Reduction of a number of cyclic trisulfide oxides to the corresponding trisulfides has been achieved using NaI in the presence of aqueous $HClO_4$ (Scheme 1.30).[27]



75 76 (80-88%)

Scheme 1.30

Treatment of **74** under the conditions reported in the literature promoted some reaction, which could be visually appreciated by the change of colour from yellow to dark orange. Analysis by TLC showed absence of starting material after 90 minutes. A new compound was formed, with an R_f identical to that of disulfide **44**. After work-up and purification by column chromatography, a sample of the product (Scheme 1.31) was submitted for ^{1}H NMR.



74 42 (67%) 44 (33%)

Scheme 1.31

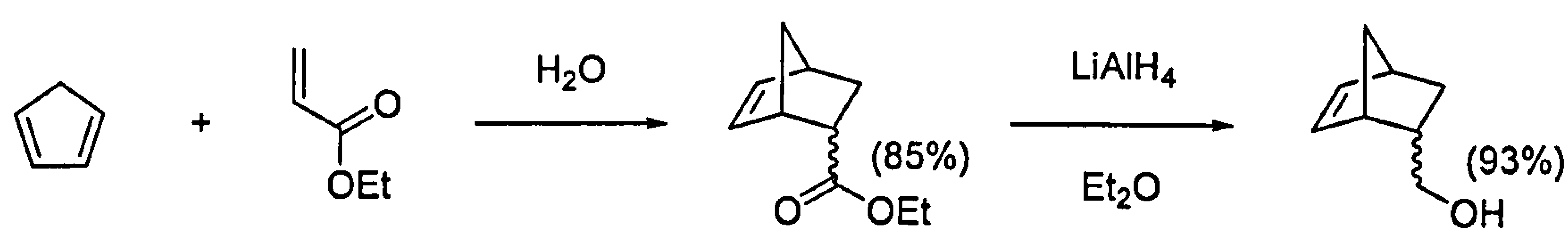
The analysis showed the presence of two compounds, one of which was characterized as disulfide **44** (33%). The other product (67%) was not the oxide **74** or thiosulfinate **52**. All the peaks were in the aromatic region and there was evidence of only three non-equivalent protons. ^{13}C-NMR and mass spectrometry confirmed the product to be the target trisulfide **42**. Several unsuccessful attempts were made to separate the two compounds (by column chromatography on extrafine silica (Ø < 0.063 mm) or recrystallisation). However, the presence of disulfide **44** was considered unlikely to be detrimental for the devised reaction (Scheme 1.10). Indeed **44** was anticipated to be one of the products of the reaction and thus expected to be present in the reaction mixture anyway. Upon repetition, the reduction of trisulfide oxide **74** gave reproducible results with quantitative conversion to a "pure" mixture of disulfide **44** and trisulfide **42** in an average ratio of 35:65, after column chromatography.

The mixture of **42** and **44** obtained was subjected to a series of conditions to test the stability of **42**. Three separate samples were dissolved in $CDCl_3$ and, respectively

1) kept in the dark at room temperature (NMR tube),
2) exposed to sunlight at room temperature (NMR tube), and
3) exposed to low-pressure Hg lamp at 254 nm (quartz cuvette).

The first sample showed no changes over the following 20h. The second one showed slow decomposition; the disulfide: trisulfide ratio varied from 1:3 to 1:2 in the next 30 hours. The third one produced a relatively quick transformation from **42** to **44**; their ratio went from 1:3 to 1:1.25 after 4 hours of irradiation.

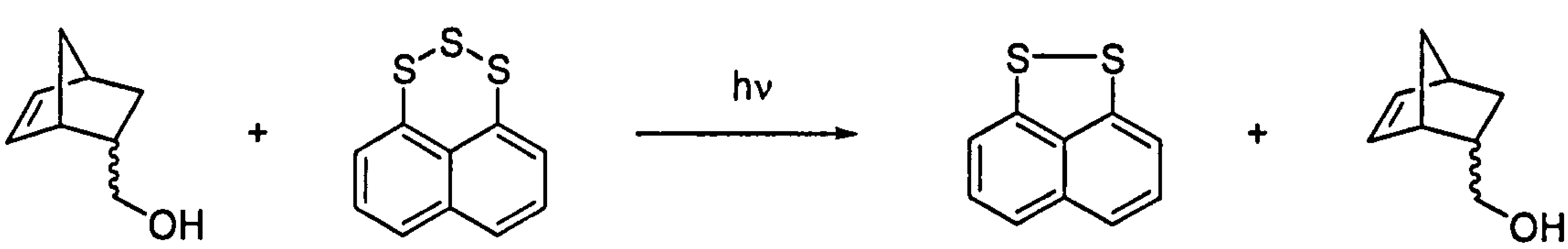
With this information in hand, we prepared a suitable strained alkene that could trap the sulfur liberated under photochemical conditions. To this aim we synthesized the norborn-2-ene derivative **80**[28] (the alcoholic moiety was introduced to visualise the compound with $KMnO_4$). Both endo and exo adducts (**80a** and **80b**) were formed in a 85:15 ratio (Scheme 1.32).



77 **78** **79a, 79b** **80a, 80b**

Scheme 1.32

Since it seemed that daylight was able to induce the desired transformation, we set up a very straightforward experiment: a mixture of **80** and **42**:**44** (71:29) was dissolved in $CDCl_3$ and irradiated with a table lamp for 30 minutes. The **42**:**44** ratio decreased to 65:35 and no other compound was detected by ^1H NMR, but for **80**. The lamp was switched off and the mixture was then left on the bench for 60 hours. Decomposition of trisulfide to disulfide was almost complete (17:83) but again no new products were formed (Scheme 1.33).

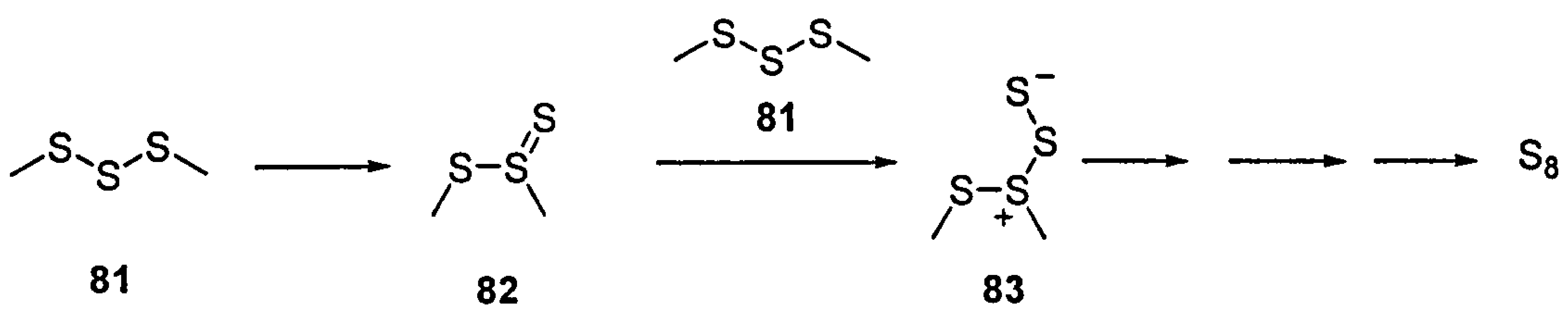


80a, 80b **42** **44** **80a, 80b**

Scheme 1.33

UV spectroscopy also indicated two absorption peaks for **42** at around 255 and 380 nm;

medium-pressure Hg lamps are known to emit strongly, among other frequencies, at 254 and 366 nm. Again, irradiation of **42** and **70** in a quartz cuvette under these conditions gave the same results as outlined in Scheme 1.33. Loss of sulfur did not come as a surprise as trisulfides are known to undergo this type of transformation.[29] Harpp suggested that thermal extrusion proceed *via* a branched thiosulfoxide intermediate **82**, which can abstract sulfur and eventually decompose to S_8 (Scheme 1.34).[30]



Scheme 1.34

The plausibility of this mechanism is reinforced by the fact that presence of elemental sulfur was routinely detected by TLC analysis.

In conclusion, in spite of the successful synthesis of the target cyclic trisulfide **34**, we were not able to achieve direct transfer of sulfur to alkene **70**.

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected.

Infra-red spectra were recorded on a Perkin-Elmer Paragon 1000 Fourier transform I.R. spectrometer.

^{1}H NMR were recorded using a Bruker AM360 or AM400 spectrometer in deuterochloroform, unless otherwise stated, referenced to TMS (δ 0). Chemical shifts are in parts per million (δ ppm). Coupling constants are in Hertz (*J* Hz). The following abbreviations are used: bs-broad singlet, s-singlet, d-doublet, dd-double doublet, t-triplet, m-multiplet.

^{13}C NMR were recorded on a Bruker AM360 or AM400 spectrometer in deuterochloroform unless otherwise stated. Chemical shifts are in parts per million (δ ppm).

Mass spectra were recorded on a Jeol AX505W spectrometer (EI).

Flash chromatography was carried out according to Still's paper[31] using Merck silica gel 60 (4063 μm). *Analytical t.l.c.* was carried out on Merck (aluminium sheets) silica gel 60 F_{254} plates using short wave (254 nm) UV light, Ninhydrin spray (from BDH), $KMnO_4$ or anisaldehyde to visualise components.

Solvents and reagents were purified as follows:

Benzene - Distilled from calcium hydride and stored over 4 Å molecular sieves.

m-CPBA – A buffer solution was prepared from 410 cm^3 of 0.1M NaOH, 250 cm^3 of 0.2M KH_2PO_4 and made up to 1 litre with distilled water. *m*-CPBA (40 g, 57-86%) was dissolved in dry ether (300 cm^3) and washed four times with the buffer. The organic phase was dried over $MgSO_4$ and carefully evaporated under reduced pressure to give ca. 20 g of pure *m*-CPBA, which was stored in the fridge.

Dichloromethane - Distilled from calcium hydride and stored over 4Å molecular sieves.

Tetrahydrofuran - Freshly distilled from sodium and benzophenone.

All other reagents and solvents were used as received.

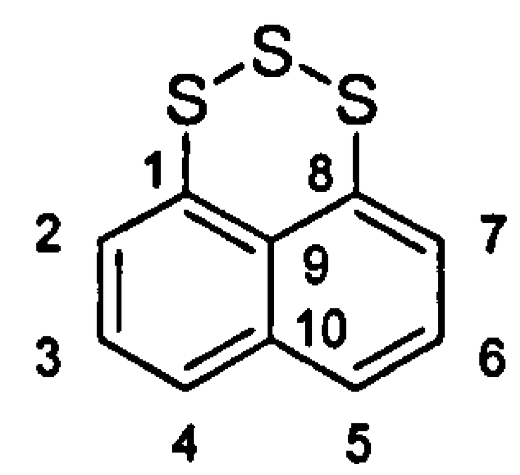
Cooling mixtures were obtained as follows:

0 °C: ice/water.

-5 °C to –78 °C: acetone/dry ice.

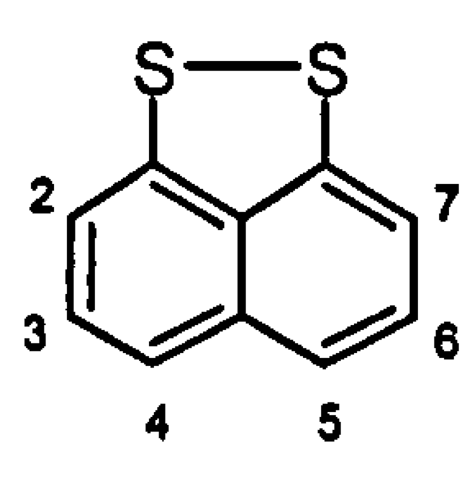
Unless otherwise stated, all reactions in non aqueous media were carried out under an atmosphere of argon in oven-dried glassware.

1,2,3-Trithia-phenalene (42).



Trisulfide 2-oxide **74** (200 mg, 0.84 mmol) was dissolved in THF (50 cm^3). A degassed solution of NaI (750 mg, 5 mmol) in H_2O (20 cm^3) was added and the mixture cooled to 0 °C. $HClO_4$ (4 M solution, 10 cm^3, 50 mmol) was syringed in dropwise and the mixture was allowed to reach room temperature. Stirring was continued for 90 mins, after which the yellow solution had turned orange. The reaction was quenched with $NaHCO_3$, extracted with dichloromethane (3 x 100 cm^3) and dried over $MgSO_4$. Purification by column chromatography (60-80 petroleum ether) gave a mixture of **42** (67%, ^{1}H NMR) and **44** (35%) as an orange crystalline solid (168 mg, 100%); R_f 0.7 (80:20 60-80 petroleum ether:diethyl ether); mp 112-114 °C (hexane); υ_{max} (CH_2Cl_2)/cm^{-1} 1644 (Ar); δ_H(360 MHz; $CDCl_3$) 7.42 (2H, dd, 3-H and 6-H, *J* 8.0 and 7.4), 7.64 (2H, dd, 2-H and 7-H, *J* 7.4 and 1.2), 7.85 (2H, dd, 4-H and 5-H, *J* 8.0 and 1.2); δ_C (100 MHz; $CDCl_3$) 116.4 (d, 4-C and 5-C), 122.1 (d, 3-C and 6-C), 125.2 (d, 2-C and 7-C), 128.3 (s, 10-C), 129.2 (s, 9-C) 131.2 (s, 1-C and 8-C); *m/z* (LREI) 222 (M^+), 190, 158, 145, 114, 95; *m/z* (HREI) calcd for $C_{10}H_6S_3$ 221.96317; found 221.96316.

[1,8-*c*,*d*]-1,2-Dithiole (44).



(I) From 1-8 diiodonaphthalene 57 via lithium-halogen exchange.[14]

1,8-Diiodonaphthalene **57** (400 mg, 1.05 mmol) was dissolved in dry THF (60 cm^3) in a two-necked round bottom flask equipped with a magnetic stirrer, a nitrogen inlet and a dropping funnel. The solution was cooled to –78 °C and a solution of butyllithium (2.5 M in hexane; 0.8 cm^3, 2.00 mmol) was added dropwise over 10 minutes. The solution turned from yellow to light orange and was stirred for a further 90 minutes. Elemental sulfur (70 mg, 2.18 mmol) was then added to the solution which was stirred for 45 minutes. The reaction was quenched by the addition of saturated ammonium chloride solution (5 cm^3) and allowed to reach room temperature. Oxygen was passed through the reaction mixture overnight, and then it was diluted with dichloromethane (10 cm^3). The organic layer was separated, washed sequentially with water and saturated sodium chloride solution, dried over $MgSO_4$ and the solvent removed under reduced pressure. The dark brown oily residue was purified by column chromatography (hexane) to afford **44** (240 mg, impure by ^{1}H-NMR) as an orange crystalline solid.

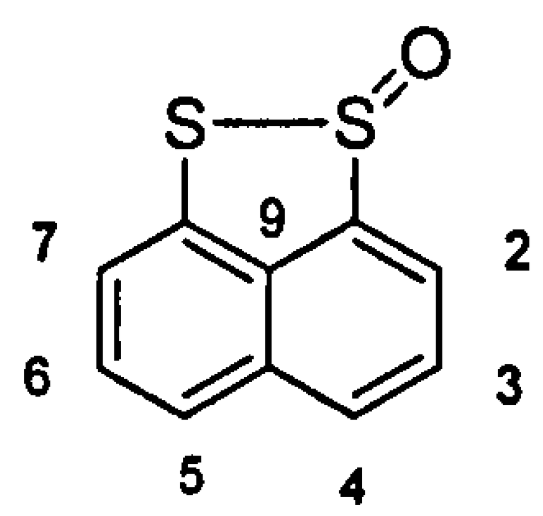
(II) From 1-8 dibromonaphthalene 66 via lithium-halogen exchange.

1,8-Dibromonaphthalene **66** (500 mg, 1.75 mmol) was dissolved in dry tetrahydrofuran (7 cm^3) in a two-neck round bottom flask equipped with a magnetic stirrer, a nitrogen inlet and a dropping funnel. The solution was cooled to –78 °C and a solution of butyllithium (2.5 M in hexane; 1.4 cm^3, 3.50 mmol) was added dropwise over 10 minutes. The solution was stirred for a further 90 minutes. Elemental sulfur (70 mg, 2.18 mmol) was then added to the solution and stirring continued for 45 minutes. The reaction was quenched by addition of saturated ammonium chloride solution (5 cm^3) and allowed to reach room temperature. Oxygen was passed through the reaction mixture overnight, and then it was diluted with dichloromethane (12 cm^3). The organic layer was separated, washed sequentially with water and saturated sodium chloride solution, dried over $MgSO_4$ and the solvent removed under reduced pressure. The dark brown oily residue was purified by column chromatography (hexane) to afford **44** (21 mg, 6%) as an orange crystalline solid.

(III) From 1-8 dibromonaphthalene 66 via Grignard.

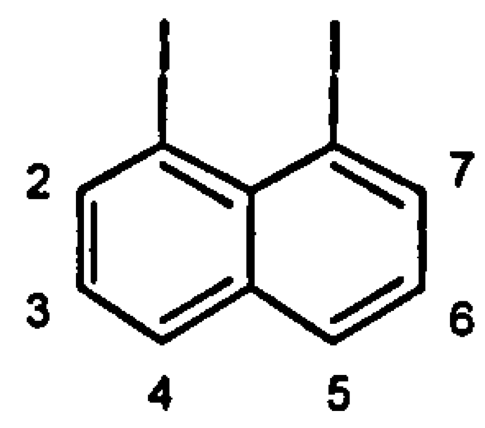
An oven-dried three-neck round bottom flask was equipped with a magnetic stirrer, a condenser, a dropping funnel and a nitrogen inlet. Magnesium turnings (3.00 g, 123.40 mmol) and a few crystals of iodine in dry THF (100 cm^3) were stirred at 65 °C until the solution turned yellow. A solution of 1,8-dibromonaphthalene **66** (3.53 g, 12.34 mmol) in tetrahydrofuran (40 cm^3) was added dropwise over 1.5 hours. The mixture was stirred for 2 h 15 minutes (the solution turned black and the majority of magnesium disappeared). It was then transferred *via* cannula to a nitrogen-filled flask containing elemental sulfur (6.00 g, 234.60 mmol) in dry tetrahydrofuran (25 cm^3) and stirred overnight (19 h) at room temperature. The reaction was quenched by addition of saturated ammonium chloride solution (5 cm^3). Oxygen was passed through the reaction mixture overnight, and then it was diluted with dichloromethane (12 cm^3). The organic layer was separated, washed sequentially with water and saturated sodium chloride solution, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by column chromatography (60-80 petroleum ether) to afford 44 (1.590 g, 67%) as an orange crystalline solid; R_f 0.4 (60-80 petroleum ether); mp 104 °C (hexane); υ_{max} (nujol)/cm^{-1} 1460 (Ar); δ_H(360 MHz; $CDCl_3$) 7.15 (2H, d, *J* 7.7 Hz, 4-H and 5-H), 7.27 (2H, t, *J* 7.7 Hz, 3-H and 6-H), 7.35 (2H, d, *J* 7.7 Hz, 2-H and 7-H); δ_C(90 MHz, $CDCl_3$) 116.0 (d, 4-C and 5-C), 121.7 (d, 3-C and 6-C) 127.9 (d, 2-C and 7-C) 134.8 (s, 10-C) 135.8 (s, 9-C), 144.1 (s, 1-C and 8-C); *m/z* (LREI) 190 (M^+; 100%), 158 (2), 126 (2), 114 (11), 95 (13).

Naphtho(1,8-cd)-1,2-dithiole 1-oxide (52).[13a]



A two neck, oven dried, 250 cm^3 round bottom flask equipped with a dropping funnel was flushed with argon. [1,8-*c*,*d*]-1,2-Dithiole (500 mg, 2.65 mmol) was dissolved in dichloromethane (50 cm^3) and cooled to 0 °C. A solution of *m*-chloroperbenzoic acid (500 mg, 2.91 mmol) in dichloromethane (50 cm^3) was added dropwise over 1 hour, keeping the temperature at 0 °C. The reaction mixture was then allowed to reach room temperature and stirred for a further 2 hours. The reaction was diluted with a saturated solution of sodium hydrogen carbonate, extracted with dichloromethane (3x50 cm^3) and dried over $MgSO_4$. Purification by column chromatography (70:30 60-80 petroleum ether: diethyl ether) gave 52 (540 mg, 99%) as a yellow crystalline solid; R_f 0.18 (70:30 60-80 petroleum ether: diethyl ether); mp 93 °C (hexane); υ_{max} (CH_2Cl_2)/cm^{-1} 1076 (SO); δ_H(360 MHz; $CDCl_3$) 7.59-7.68 (2H, m, 3-H and 6-H), 7.81 (1H, d, *J* 7.1, 4-H), 7.82 (1H, d, *J* 8.0, 5-H), 8.15 (1H, d, *J* 8.0, 2-H), 8.20 (1H, d, *J* 7.1, 7-H); δ_C (100 MHz; $CDCl_3$) 122.4 (d, 3-C or 6-C), 125.0 (d, 5-C), 127.8 (d, 7-C), 128.1 (d, 4-C), 129.2 (d, 3-C or 6-C), 132.2 (d, 2-C), 133.9 (s, 10-C), 134.0 (s, 9-C), 137.9 (s, 8-C), 149.1 (s, 1-C); *m/z* (LREI) 206 (M^+; 100%), 190 (20), 177 (44), 174 (17), 158 (13), 134 (18).

1,8-Diiodonaphthalene (57).



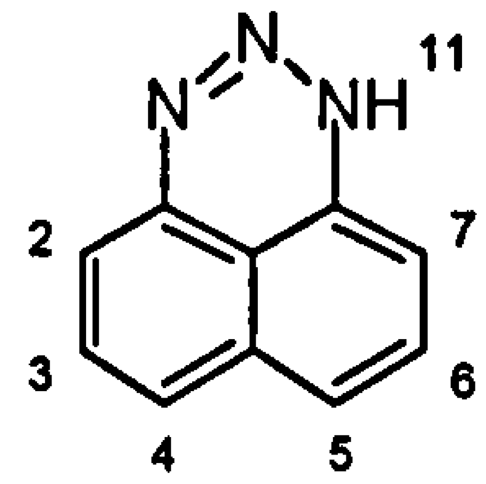
(I) From 1,8-diaminonaphthalene 59.[17]

1,8-Diaminonaphthalene **59** (1.5 g, 9.50 mmol) was suspended in H_2SO_4 (50 cm^3, 6.9 M) in a round bottom flask equipped with an overhead stirrer, a thermometer and a dropping funnel. The mixture was cooled to –20 °C and an aqueous solution (20 cm^3) of $NaNO_2$ (1.92 g, 27.85 mmol) was added dropwise, keeping the temperature between –15 °C and –20 °C. As soon as the addition was complete, an aqueous solution (25 cm^3) of KI (9.64 g, 58.03 mmol) was added dropwise with stirring, keeping the temperature in the same range. The resulting mixture was heated rapidly to 80 °C and then allowed to cool to room temperature. The solution was made alkaline by the addition of NaOH pellets and filtered. The solid residue was left to stand overnight and then extracted (Soxhlet) with diethyl ether for 24 hours. The ethereal solution was successively washed with 10% HCl, saturated aqueous $Na_2S_2O_3$ and 10% aqueous NaOH, dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting brown powder was purified by recrystallisation (hexane) to give **48** (500 mg, 14%) as a white crystalline solid.

(II) From naphtho[1,8-*de*]triazine 65.

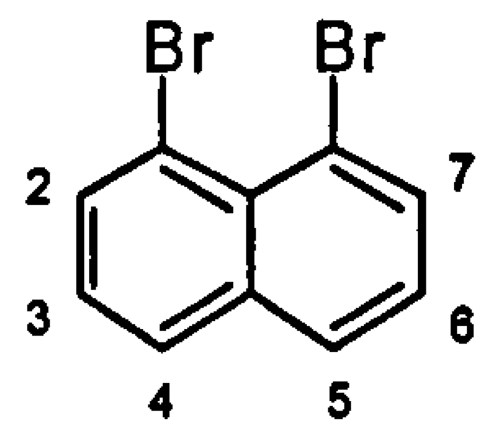
Naphtho[1,8-*de*]triazine (6.15g, 36.40 mmol) was suspended in H_2SO_4 (100 cm^3, 6.9 M) in a three-necked round bottom flask equipped with an overhead stirrer, a thermometer and a dropping funnel. The mixture was cooled to –5 °C and an aqueous solution (50 cm^3) of $NaNO_2$ (3.15 g, 45.50 mmol) was added dropwise over 15 minutes, keeping the temperature at –5 °C. After stirring the solution for 2 h at the same temperature, an aqueous solution (50 cm^3) of KI (13.30 g, 40.40 mmol) was added dropwise. The mixture was allowed to reach room temperature, stirred for 30 minutes, heated to 75 °C and stirred for a further 2.5 hours. The dark brown suspension was cooled to room temperature and set aside overnight. The pH was adjusted to 7 by the addition of NaOH pellets. The resulting precipitate was collected by filtration, washed several times with cold water and then added to ether (100 cm^3). The insoluble residues were removed by filtration and washed thoroughly with additional ether. The filtrate was dried over $MgSO_4$ and evaporated *in vacuo*. The resulting powder was purified by silica chromatography (60-80 petroleum ether) to afford **48** (4.43 g, 32%) as a white crystalline solid. R_f 0.35 (60-80 petroleum ether); mp 109-110 °C (ethanol); δ_H (360 MHz; $CDCl_3$) 7.09 (2H, t, J 7.7 Hz, 3-H and 6-H), 7.85 (2H, dd, J 7.7 and 1.1 Hz, 4-H and 5-H), 8.43 (2H, dd, J 7.7 and 1.1, 2-H and 7-H); δ_C (100 MHz, $CDCl_3$) 96.4 (s, 1-C and 8-C), 127.4 (d, 4-C and 5-C) 131.4 (s, 10-C) 132.5 (d, 3-C and 6-C) 136.2 (d, 2-C and 7-C), 144.4 (s, 9-C); *m/z* (LREI) 380 (M^+; 100%), 253 (33), 190 (11), 123 (60), 104 (24).

Naphtho[1,8-*de*]triazine (65).[21]



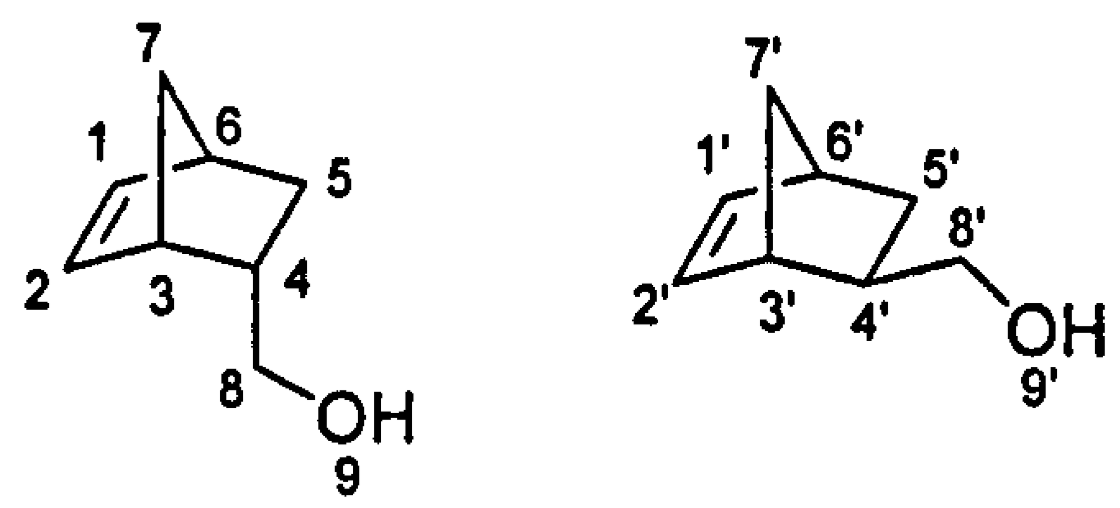
1,8-Diaminonaphthalene (16.36 g, 103.5 mmol) was dissolved in 1:1 ethanol/glacial acetic acid (100 cm^3) in a two-neck round bottom flask and the solution was cooled to 0 °C. To this, isoamyl nitrate (12.12 g, 103.5 mmol) was added dropwise. The resulting mixture was set aside overnight and then the resulting precipitate was collected by precipitation, washed thoroughly with ether, to give **56** (16.72 g, 96%) as a brown powder; mp 180 °C (ethanol - decomposition); υ_{max} (nujol)/cm^{-1} 1461 (Ar), 1572 (N=N); δ_H (360 MHz; d_6-DMSO) 7.15-7.24 (6H, m, 2-H to 7-H), 13.3 (1H, s, 11-H); *m/z* (LREI) 169 (M^+; 42%), 141 (100), 140 (52), 114 (58), 70 (14).

1,8-Dibromonaphthalene (66).[22]



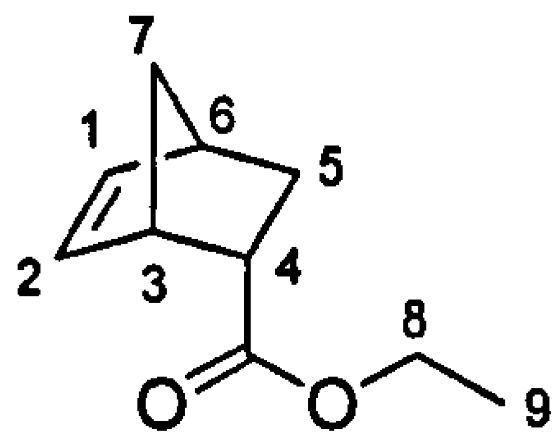
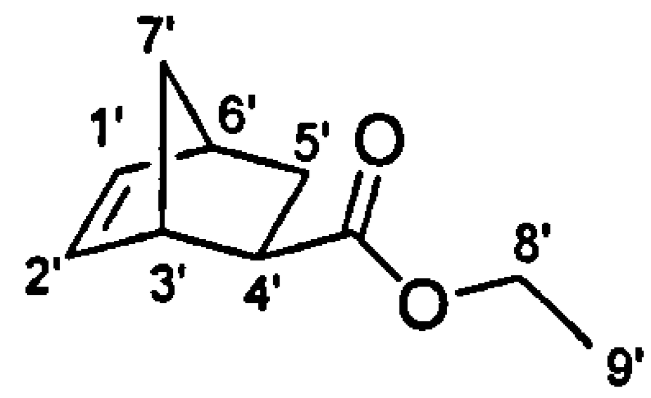
Naphtho[1,8-*de*]triazine **65** (6.15g, 36.4 mmol) was suspended in H_2SO_4 (50 cm^3, 6.9M) in a three-neck round bottom flask, equipped with an overhead stirrer, a thermometer and a dropping funnel. The mixture was cooled to –5 °C and an aqueous solution (20 cm^3) of $NaNO_2$ (3.15 g, 45.5 mmol) was added dropwise over 20 minutes, mantaining the temperature at –5 °C. After stirring the solution for 2 h at the same temperature, a solution of CuBr (18.80 g, 65.5 mmol) in HBr (50 cm^3, 45% in CH_3COOH) was added dropwise. The mixture was warmed to room temperature, heated to 90 °C and stirred for a further 2.5 hours. The dark brown suspension was cooled to room temperature and the pH was adjusted to 7, by addition of NaOH pellets. The resulting precipitate was collected by filtration, washed several times with cold water and then added to ether (100 cm^3). The insoluble residues were removed by filtration and washed with additional ether. The filtrate was dried over $MgSO_4$ and evaporated *in vacuo*. The resulting powder was purified by silica chromatography (60-80 petroleum ether) to afford **57** (3.96 g, 38%) a white crystalline solid; R_f 0.33 (60-80 petroleum ether); mp 106 °C (ethanol); υ_{max} (nujol)/cm^{-1} 749 (C-Br), 1547 (Ar); δ_H(360 MHz; $CDCl_3$) 7.28 (2H, dd, *J* 8.2 and 7.5, 3-H and 6-H), 7.83 (2H, dd, *J* 8.2 and 1.2, 4-H and 5-H), 7.96 (2H, dd, *J* 7.5 and 1.2, 2-H and 7-H); δ_C(90 MHz, $CDCl_3$) 119.9 (s, 1-C), 126.7 (d, 4-C and 5-C), 129.3 (s, 10-C) 129.9 (d, 3-C and 6-C) 135.7 (d, 2-C and 7-C), 137.5 (s, 9-C); *m/z* (LREI) 288/286/284 (M^+; 53/100/55%), 207/205 (24/24), 126 (37), 63 (20).

5-Norbornene-2-*endo*-ethanol (80a) and 5-norbornene-2-*exo*-ethanol (80b).[28]



80a **80b**

A 2-litre round bottom flask was equipped with an overhead mechanical stirrer and charged with freshly distilled cyclopentadiene (14.86 g, 225 mmol) and ethyl acrylate (15.60 cm^3, 173 mmol). The mixture was dispersed in distilled water (1.4 L) and stirred vigorously for two days. The solution was then saturated with NaCl (20 g), extracted with diethyl ether (3 x 300 cm^3) and the combined organic layers washed with brine (200 cm^3) and then dried over $MgSO_4$. Purification by distillation (62 °C, 6 mmHg) yielded a mixture of 5-norbornene-2-*endo*-carboxylic acid ethyl ester **79a** and 5-norbornene-2-*exo*-carboxylic acid ethyl ester **79b** (8:1 ratio) as a colorless oil (24.5 g, 85%).

79a **79b**

R_f 0.45 (80:20 60-80 petroleum ether:ethyl acetate); δ_H(360 MHz; $CDCl_3$) (**77a**) 1.14-1.21 (4H, m, 7-H and 9-H), 1.33-1.37 (1H, m, 6-H), 1.79-1.86 (1H, m, 3-H), 2.83-2.89 (2H, m, 5-H), 3.14 (1H, m, 4-H), 3.97-4.04 (2H, m, 8-H), 5.84-5.87 (1H, m, 1-H or 2-H), 6.10-6.13 (1H, m, 1-H or 2-H).

In a 500 cm^3 round bottom flask a suspension of $LiAlH_4$ (1.351 g, 35.60 mmol) in diethyl ether (40 cm^3) was added dropwise of a solution of **79a** and **79b** (5.909 g, 35.60 mmol) in diethyl ether (100 cm^3) over 1 hour. The reaction was then heated at reflux for 6 hours. The flask was cooled to room temperature and the reaction was quenched with 10% H_2SO_4 (50 cm^3). After extraction with diethyl ether (3 x 50 cm^3) and washing with brine (2 x 50 cm^3), the resulting organic solution was dried over $MgSO_4$. Purification by distillation (107 °C, 3 mmHg) gave a mixture of **80a** and **80b** (4.092 g, 93%, 8:1 ratio) as a colourless oil; R_f 0.1 (80:20 60-80 petroleum ether: ethyl acetate); υ_{max} (nujol)/cm^{-1} 3614 (OH); δ_H(360 MHz; $CDCl_3$) (**80a**) 0.5-0.55 (1H, m,), 1.26-1.31 (2H, m), 1.44-1.47 (1H, m), 1.79-1.86 (1H, m), 2.25-2.34 (1H, m), 2.82 (1H, bs), 2.93 (1H, bs), 3.23-3.40 (1H, m), 3.54-3.96 (1H, m), 5.95-5.98 (1H, m), 6.14-6.16 (1H, m); δ_C (100 MHz; $CDCl_3$) 29.2 (s), 41.9 (s), 42.6 (s), 43.9 (s), 49.9 (s) 66.7 (s), 132.5 (s), 137.8 (s); *m/z* (LREI) 124 (M^+; 4%), 101 (7), 91 (6), 66 (100), 65 (6); *m/z* (HREI) calcd for $C_8H_{12}O$ 124.08882; found 124.08947.

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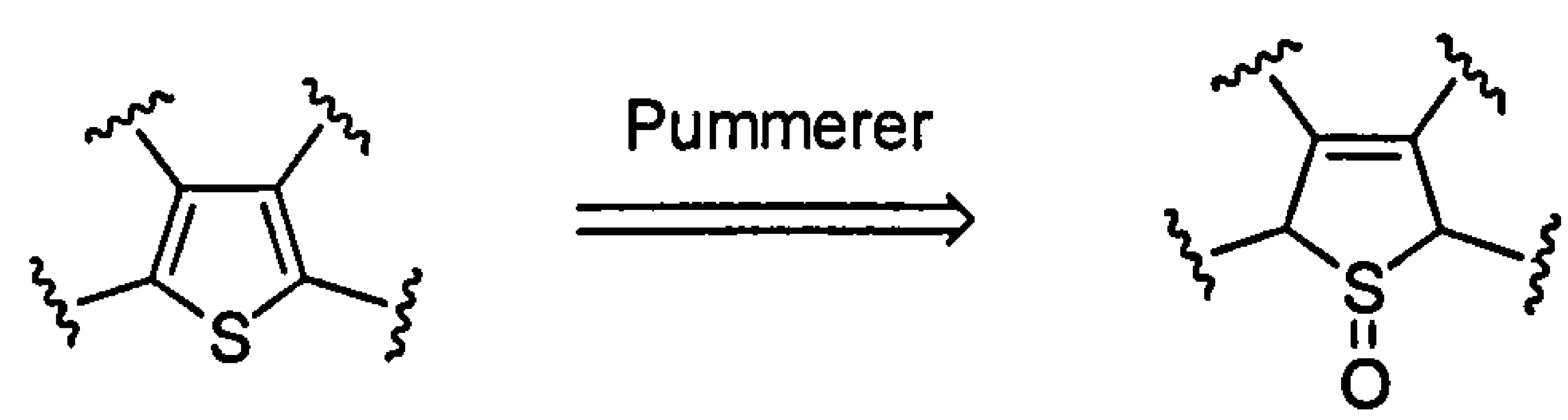
CHAPTER II:

A Novel and Recyclable Source of Sulfur Monoxide

BACKGROUND AND SIGNIFICANCE

2.1.1. 1,4-Dihydrothiophene S-oxides.

1,4-Dihydrothiophene S-oxides **2** are a family of compounds of interest in organic chemistry. When unsymmetrically substituted, the tetrahedral configuration at sulfur leads to it being a stereogenic centre and the sulfoxide functionality provides reactivity towards numerous transformations; α-hydrogens, for instance, are acidic enough to be deprotonated with strong bases. The so-formed α-sulfinyl carbanions can undergo a large array of reactions.[1] Furthermore, 1,4-dihydrothiophene S-oxides are susceptible to electrophilic attack. Since the sulfoxide group is an ambident nucleophile, attack could, in principle, occur both at sulfur and oxygen. In practice, attack on oxygen almost always predominates, furnishing an alkoxysulfonium salt.[2] Among the possible reaction of these intermediates, a variation of the Pummerer reaction is noteworthy: this specific reaction is formally a dehydration that leads to thiophenes **1** (Scheme 2.1).

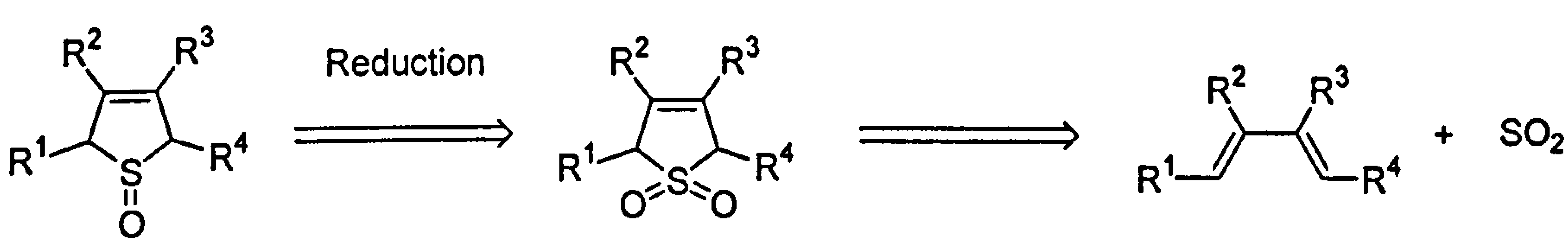


1 2

Scheme 2.1

These, in turn, have their own role in modern organic chemistry; they have found use, for instance, as building blocks for novel polymers with unusual properties.[3]

Compounds of the type **2** could in principle be obtained first by the trapping of SO_2 by 1,3-dienes **4**[4] and then by partial reduction of the sulfone **3** to the sulfoxide **2** (Scheme 2.2).



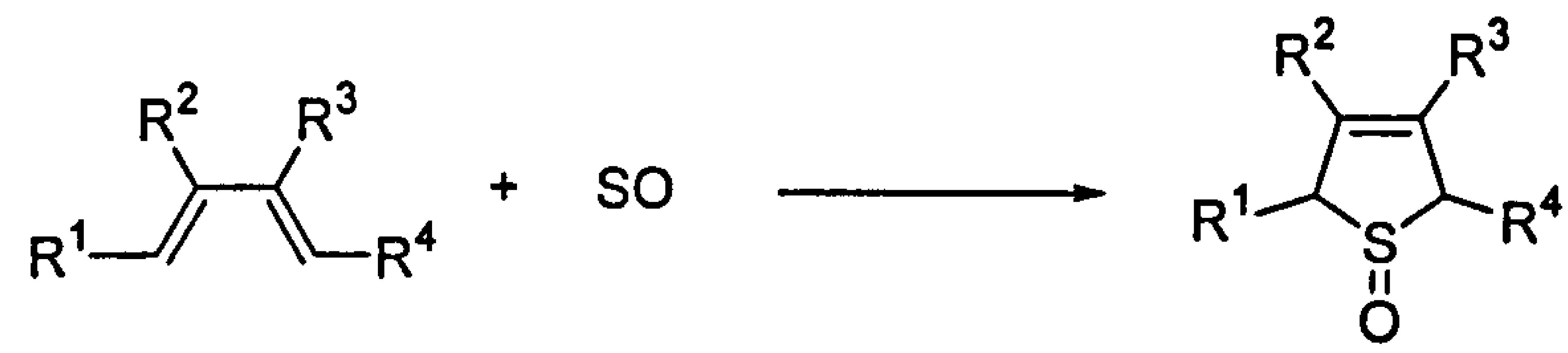
2 3 4 5

Scheme 2.2

SO_2 is an appealing choice of reagent being a cheap, commercially available source of sulfur. It is produced on very large scale by combustion of sulfur or H_2S or by roasting sulfide ores (especially pyrite, FeS_2).[5] The reduction of sulfones to sulfoxides is however far from trivial.[6]

2.1.2. Sulfur Monoxide: Synthetic Uses and Mechanism of Reaction.

A more attractive way of synthesizing **2** is the direct trapping of dienes with the diatomic molecule sulfur monoxide **6** (Scheme 2.3).

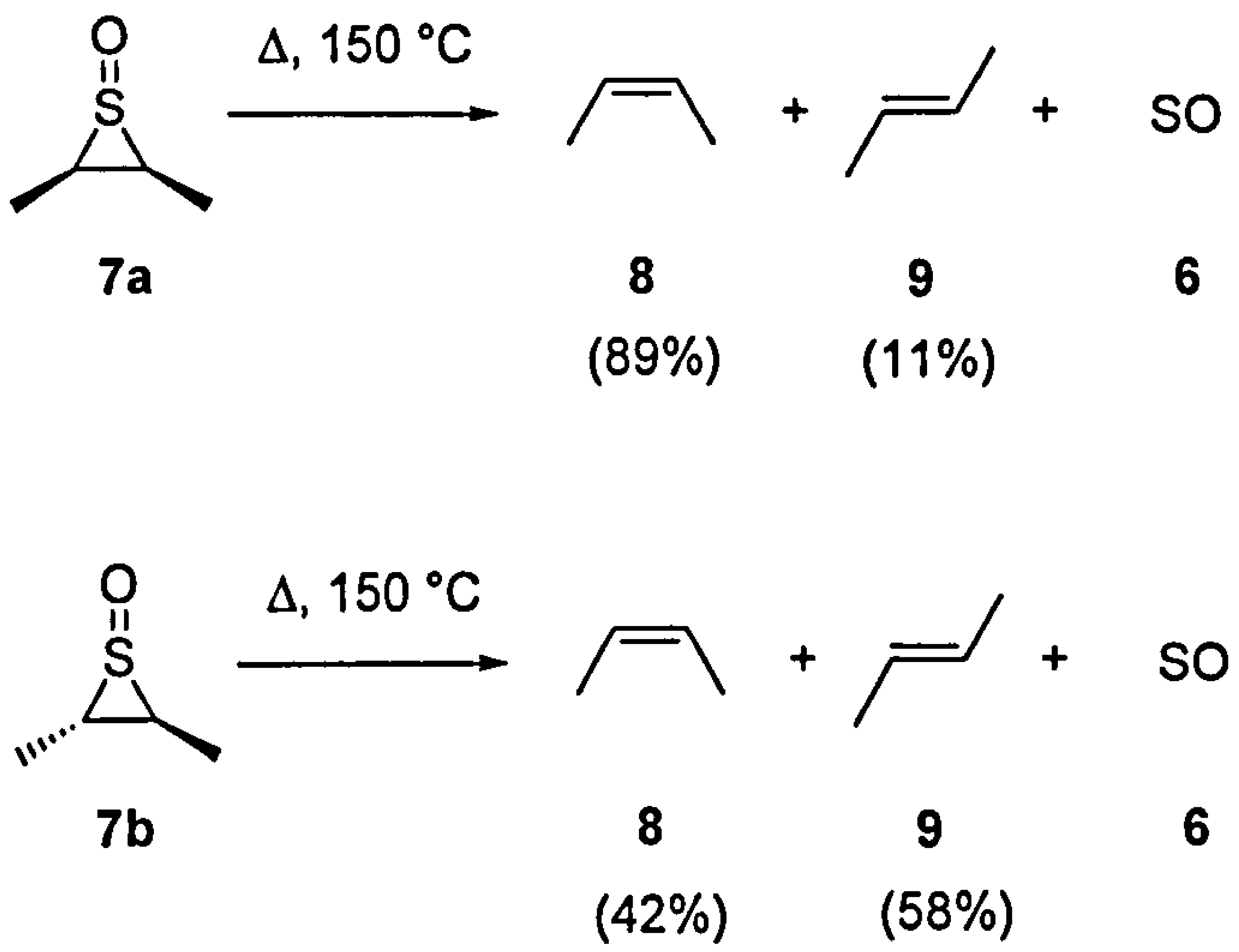


4 **6** **2**

Scheme 2.3

The UV spectrum of **6** was first observed in 1929, when it was formed by the reduction of SO_2 with sulfur vapor in a glow discharge.[5] Its close electronic relationship to O_2 (they both are in the $^3\Sigma^-$ ground state) has prompted further spectroscopic studies.[7] Unfortunately this species is thermodynamically unstable. It is known to decompose in the gas phase in less than one second into SO_2 and S_2O (*vide infra*);[5] Shenck and Steudel reported it to possess a half-life of 20 ms.[7a]

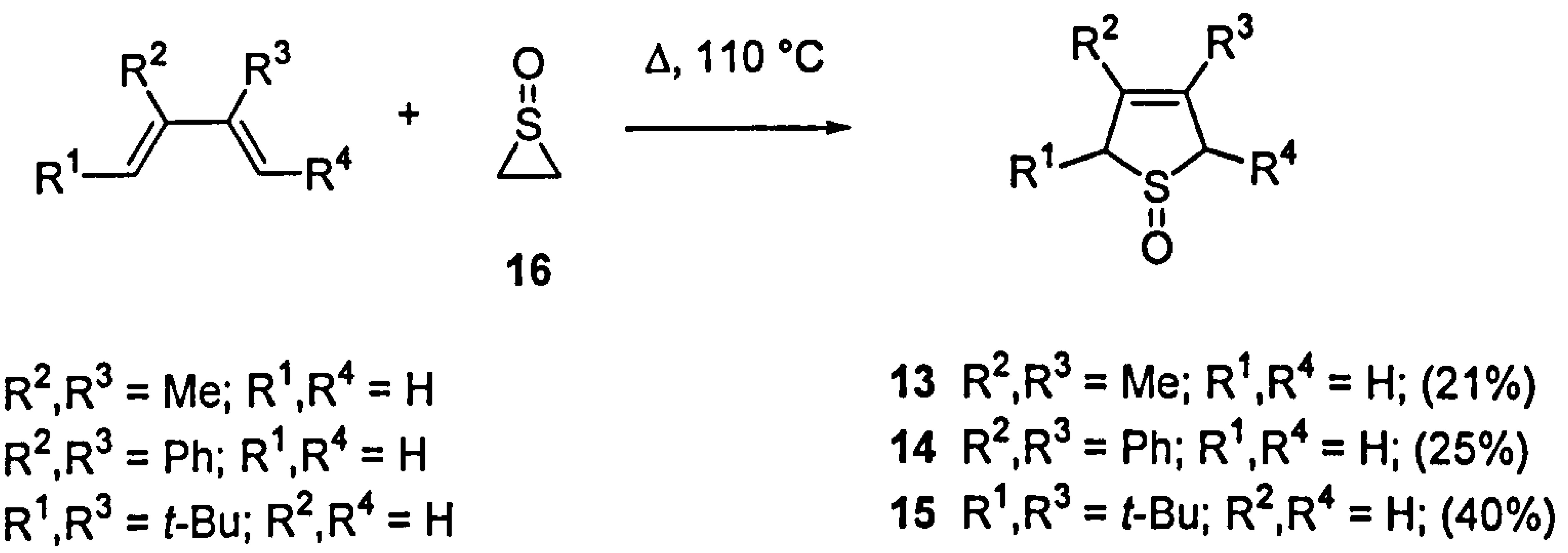
Hartzell and Paige were the first to describe the synthesis of a molecule able to "release" sulfur monoxide.[8] Mass spectroscopy and differential thermal analysis confirmed that thermal decomposition of 2-butene episulfoxides **7a** and **7b** (from the oxidation of the corresponding episulfide)[9] led to the formation of *cis*- **8**, *trans*- 2-butene **9** and SO (Scheme 2.4).



Scheme 2.4

Formation of mixture of *cis*- and *trans*- 2-butene independently from from both *cis*-7 and *trans*-7a ruled out a mechanism involving simultaneous cleavage of the two carbon-sulfur bonds. Instead the results could be explained by the steric requirements of an intermediate resulting from a two-step E1-type elimination mechanism.

Shortly after Dodson and Sauers[10] pioneered the use of 1,3-dienes as a mean of trapping sulfur monoxide; extending the work by Hartzell and Paige, they reported the formation of cyclic sulfoxides derivatives through the thermal decomposition of ethylene episulfoxide **16** (Scheme 2.5).



Scheme 2.5

The methodology was limited to a few examples and the yields were synthetically unsatisfactory, yet it stimulated the search for more effective "SO-transfer" molecules and revitalized the debate on their mechanism of action. In the same paper they argued that the sulfur monoxide reacting with the dienes would have not necessarily been in its $^3\Sigma^-$ ground state, but it could have been either in the $^1\Sigma^+$ or even in the $^1\Delta$ state.

In order to shed light on the latter point Saito analyzed the product of pyrolysis of ethylene episulfoxide by microwave spectroscopy.[11] The study led to a number of interesting conclusions. The absence of signals characteristic of ethylene sulfide and ethylene oxide strongly suggested that the abscission of the S-O bond is not the main reaction in the thermal decomposition. The author therefore concluded that the compound decomposes into ethylene and SO. Absorption lines characteristic of SO in its ground state were indeed observed at different temperatures. In principle, the $^1\Delta$ state (18.2 kcal/mol) is within reach, since the heat of decomposition of ethylene episulfoxide is estimated to be about 35-39 kcal/mol (Figure 2.1).[12]

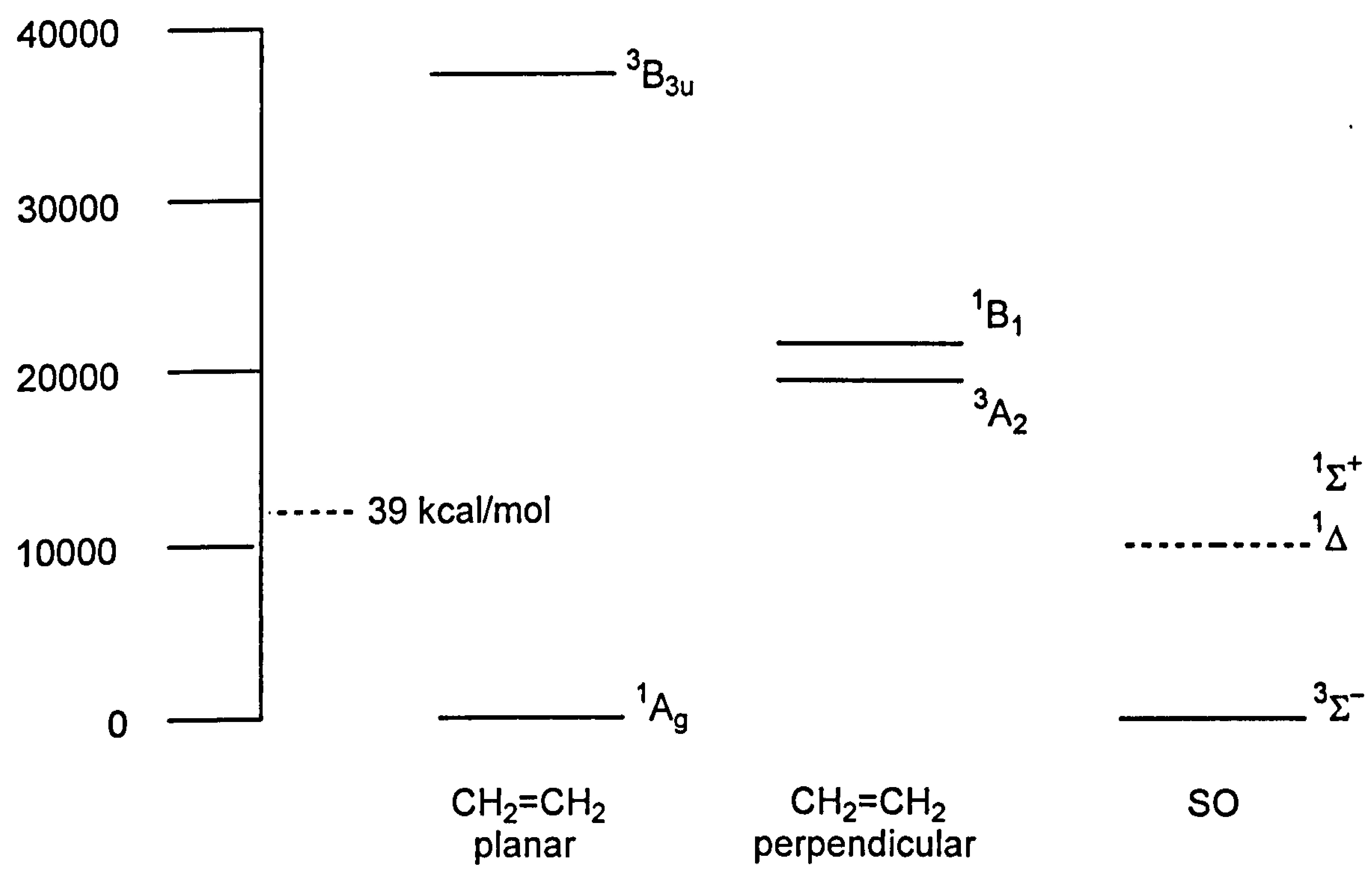
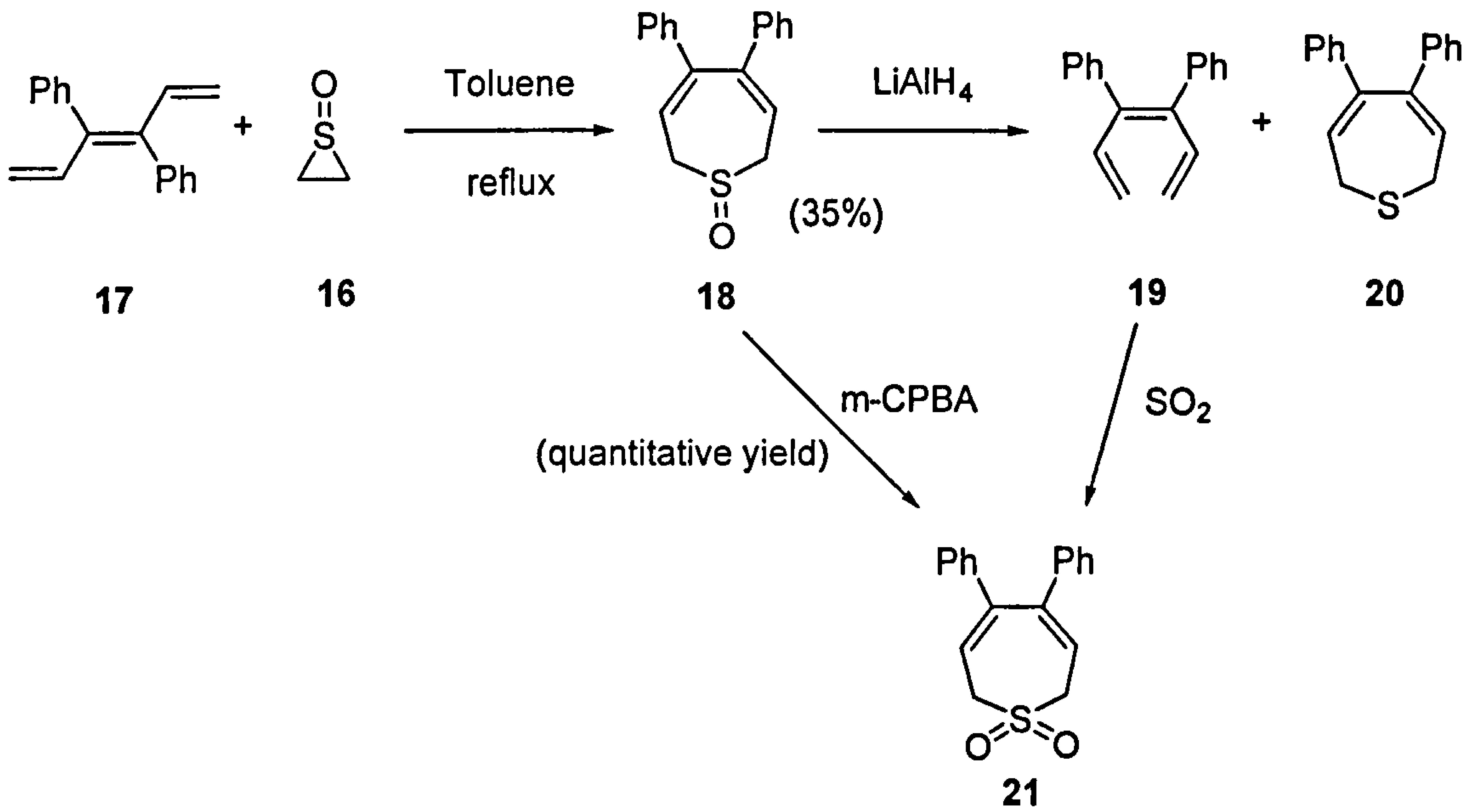


Figure 2.1

It was postulated that the $^1\Delta$ lifetime should be long enough for detection because the transition between $^1\Delta$ and $^3\Sigma^-$ is a forbidden one.[11] Also, the radiative lifetime of O_2 in the $^1\Delta_g$ state is about 45 minutes.[13] However Uehara searched for the $^1\Delta$ EPR line of SO in the pyrolysis of ethylene episulfoxide, unsuccessfully.[11] Saito concluded that the mechanism of decomposition yields both ethylene and SO in the ground state. No conclusive proof that the $^1\Sigma^+$ state (30.05 kcal/mol) was extraneous to the reaction was given. Nishitani, employing vacuum ultraviolet photoionization spectroscopy, supported these findings.[14]

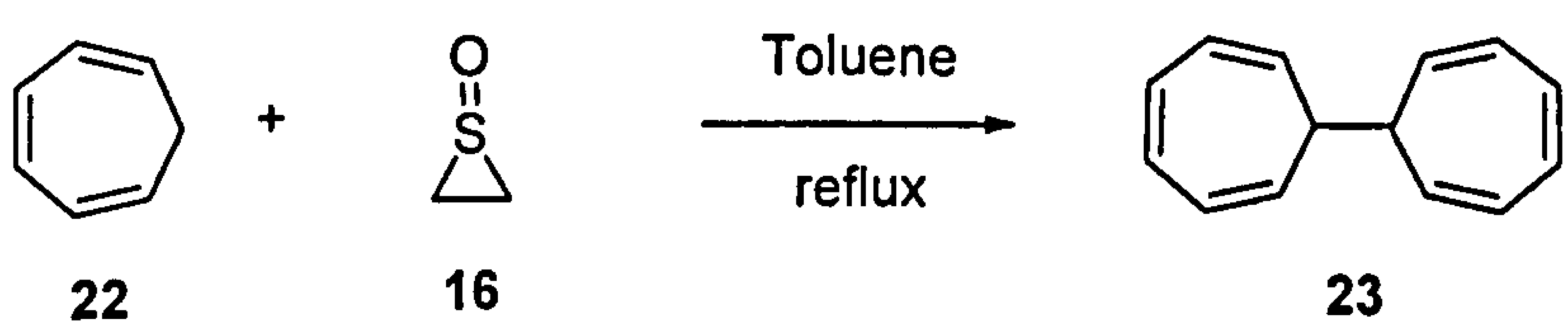
Further evidence of the validity of the speculation that the main active species is in the $^3\Sigma^-$ state was offered again by Dodson. In 1969 he published a communication in which he reported the trapping of SO by trienes (Scheme 2.6).[15]



Scheme 2.6

trans-3,4-Diphenylexa-1,3,5-triene **17** was reacted with an equimolar quantity of ethylene episulfoxide **16** in refluxing toluene to yield the cyclic sulfoxide **18**. A trapping experiment on **17** using SO_2 met with failure. $LiAlH_4$ reduction of **18** gave a mixture of cyclic sulfide **20** and triene **19**. Trapping of the latter with SO_2 was in this case successful. Sulfone **21** was compared with the compound obtained by the oxidation of **18** and found to be spectroscopically comparable.

More interesting, however, was the reaction of ethylene episulfoxide **16** with cyclohepta-1,3,5-triene **22** (Scheme 2.7).



Scheme 2.7

The resulting dihydroheptafulvalene **23** was obtained in very low yield (7%), but presumed to result from the coupling of an intermediate radical, thus underlining the role of the $^3\Sigma^-$ state as the active species.

Four years later Chao and Lamal investigated the stereochemical implications of SO trapping by dienes, extending the scope of the reaction.[16] The group used the 2,4-hexadiene isomers (*tt*-**24**, *ct*-**25** and *cc*-**26**) to trap the thermally generated SO. The three possible sulfoxides **27**, **28** and **29** were isolated in variable yields (34-42%) and characterized (Table 2.1).

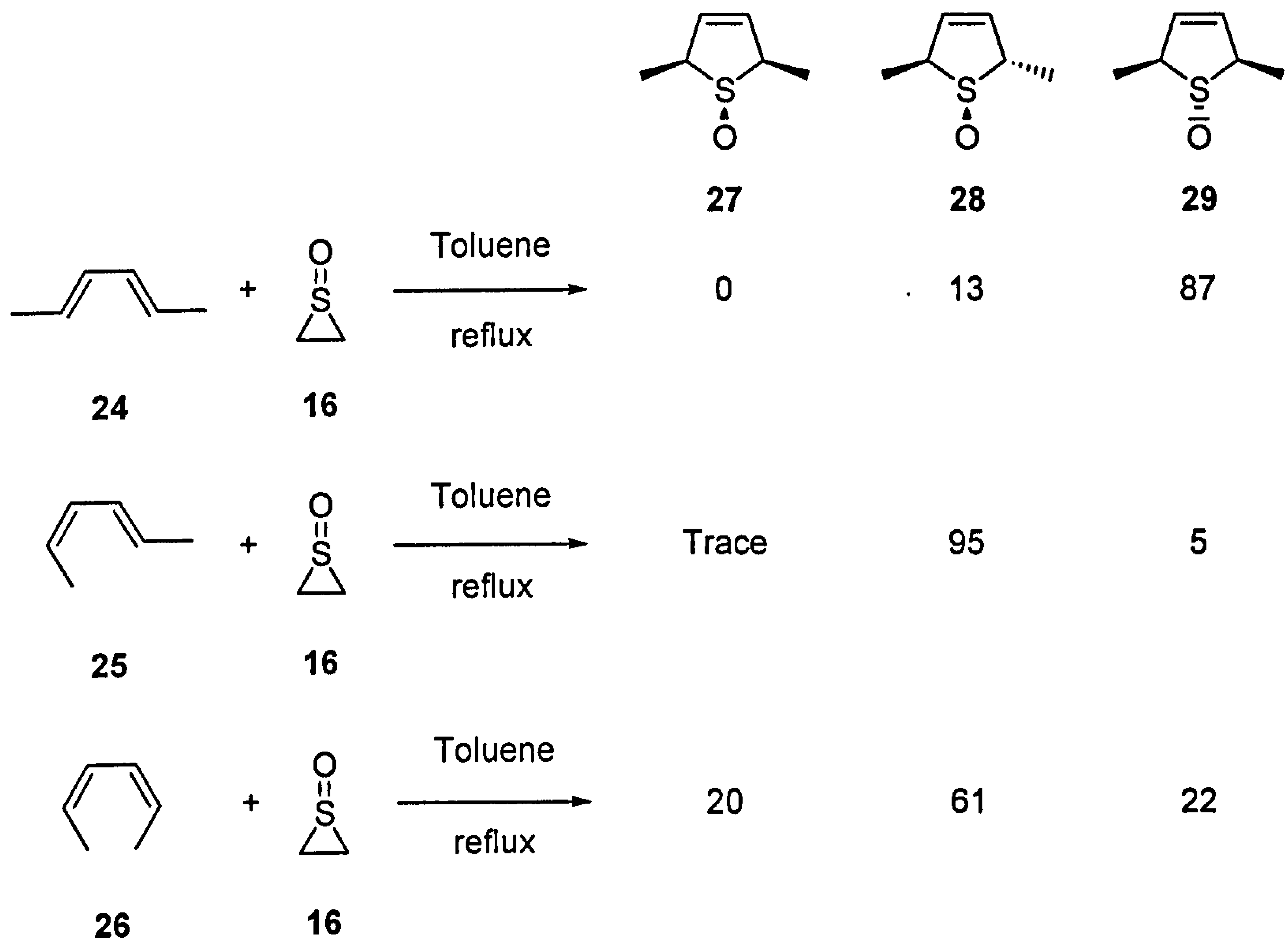
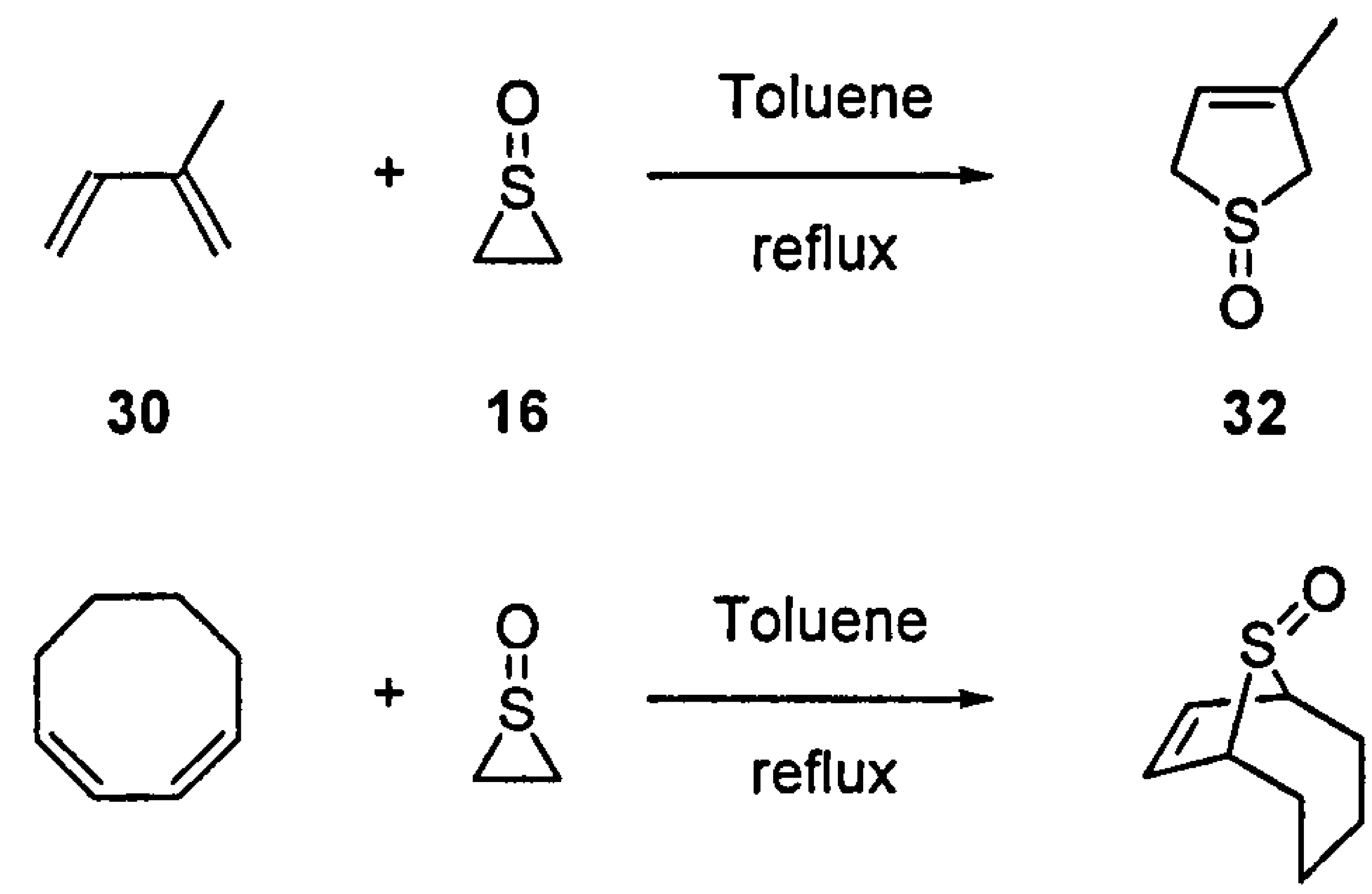


Table 2.1

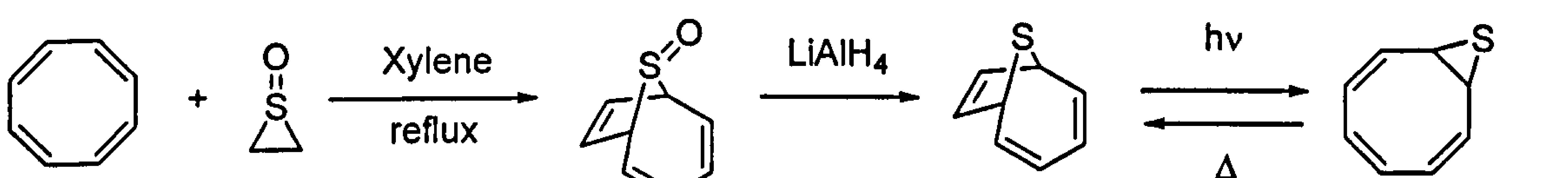
Thermal interconversion experiments revealed that the order of stability was **27** > **28** > **29**. This was confirmed by treatment of **29** with hydrogen chloride in dioxane (which equilibrates sulfoxides at sulfur) to give almost exclusively **27**. Nevertheless high stereoselectivity was observed with **24** and **25**. Stereoselectivity at sulfur is detectable exclusively in *cis*- methyl-sulfoxides; surprisingly SO addition to **24** leads to the less stable *cis*- methyl-sulfoxide **29**. Explanation of this unexpected behaviour was provided in a follow up paper. The same authors demonstrated without any further doubt that $^3\Sigma^-$ has to be considered the reacting species in the thermal decomposition of **16.**[17] They presented arguments for a radical process, rather than an ionic one. The mechanism proposed accounted for the formation of a singlet intermediate first that through intercrossing system would rapidly equilibrate to the triplet state. This view was later supported by Baldwin[18] and Glass.[19] Also, trapping was reported in the case of two new dienes, namely isoprene (2-methyl-1,3 butadiene) in 72% yield and 1,3-cyclooctadiene (no yield reported) (Scheme 2.8).



Scheme 2.8

The chemistry of the ($^1\Sigma^+$) and the ($^1\Delta$) SO vibronic levels induced by near-infrared light was subsequently explored by Frei.[20] He demonstrated that the only spin conserved and orbital allowed [1+2] reaction was the addition to alkenes to form episulfoxides.

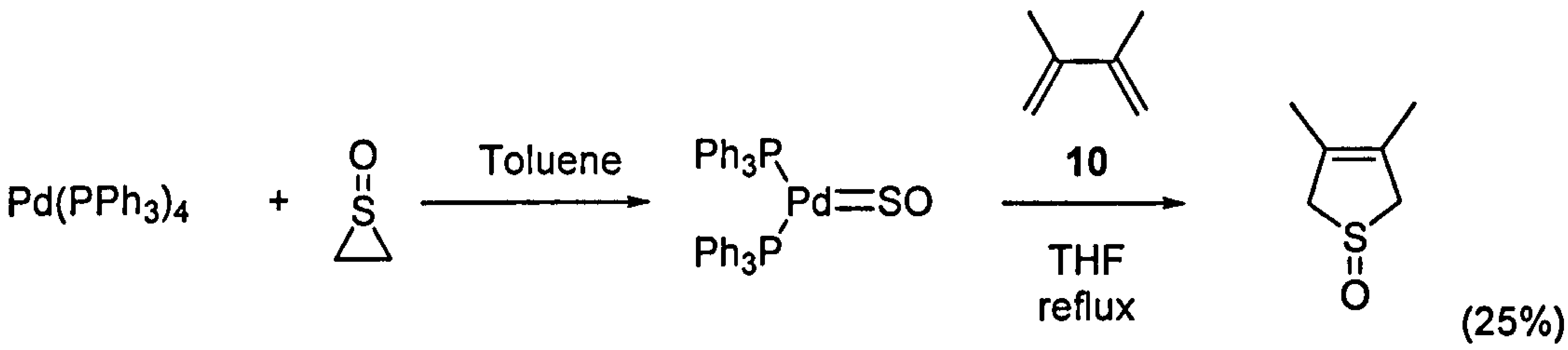
Anastassiou broadened scope of this reaction,[21] with the formation and photochemical isomerization of oxathia-bicyclo[4,2,1]nonatriene **35** in a novel route to the synthesis of 9-thiabicyclo[6,1,0]nona-2,4,6-triene **37** (Scheme 2.9).



Scheme 2.9

Weiner studied the photochemistry of ethylene episulfoxide **16**.[22] He concluded that: (1) **16** undergoes photoelimination of SO diradical **6** in the $^3\Sigma^-$ ground state; (2) there are strong indications that SO is produced by concerted cleavage of the two C-S bonds; and (3) Frank-Condon and impulsive physical models show that the other product of the reaction is triplet and not ground-state ethylene.

The main problem with the use of ethylene episulfoxide **16** as a "SO transfer" molecule is its inherent instability, the disagreeable odor and the fact that it causes skin burns.[23] Schenk[24] and Heyke[25] proposed metal coordination as a solution to improve its manageability (especially the stability). Pyrolysis of **16** in the presence of some Rh, Ir and Pd complexes led to the formation of a new class of SO-containing complexes that can be easily handled. Heyke in addition tested his complex in a trapping experiment with 2,3-dimethyl-1,3-butadiene **10**, with no encouraging results. One such example is depicted in Scheme 2.10.

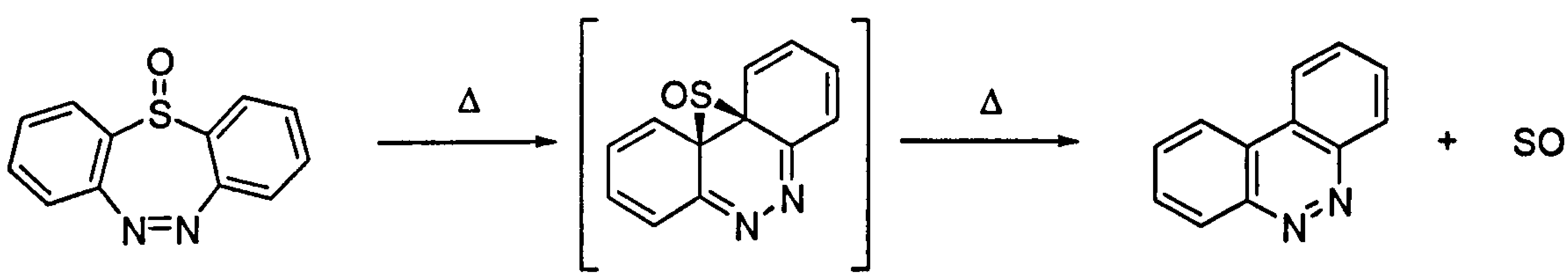


38 **16** **39** **13**

Scheme 2.10

Other authors later confirmed the extremely limited applicability of all these complexes as a source of SO.[26]

The first group to propose an alternative source of SO was that of Chow and co-workers.[27] In 1970 they presented evidence that disrotatory electrocyclisation of dibenzo {*b,f*}[1,4,6]thiadiazepin-1-oxide **40** leads to the formation of benzocinnoline **42**, elemental sulfur and SO_2. They invoked the formation of intermediate **41** and its disproportionation to account for the formation of the latter two species (Scheme 2.11).

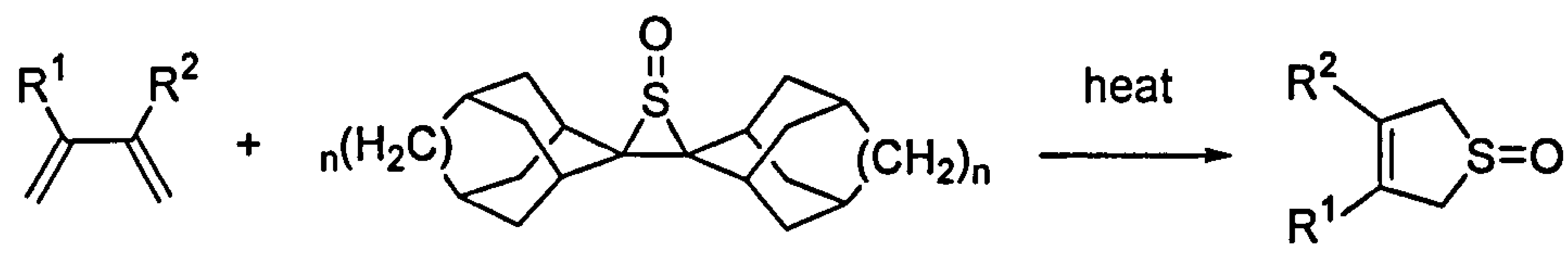


40 **41** **42** **6**

Scheme 2.11

In fact thermal decomposition of **40** in the presence of 2,3-diphenylbutadiene **11** and 1,3-cyclooctadiene **31** yielded the corresponding cyclic **14** and bicyclic **33** sulfoxides, although in unsatisfactory yields (30 and 19%, respectively).

It was not until 1997 that a more widely applicable source of SO was introduced.[22] Harpp and co-worker prepared the structurally fascinating episulfoxides **43** and **44** by m-CPBA oxidation of the corresponding episulfides. Thermal decomposition of both **43** and **44** in the presence of four different 1,3 dienes **10, 11, 30** and **45** gave excellent results in terms of isolated yields of 1,4-dihydrothiophene S-oxides (Scheme 2.12).



10; R^1, R^2=Me
11; R^1, R^2=Ph
30; R^1=Me, R^2=H
45; R^1=$(CH_2)_2CH$=$C(CH_3)_2$, R^2=H

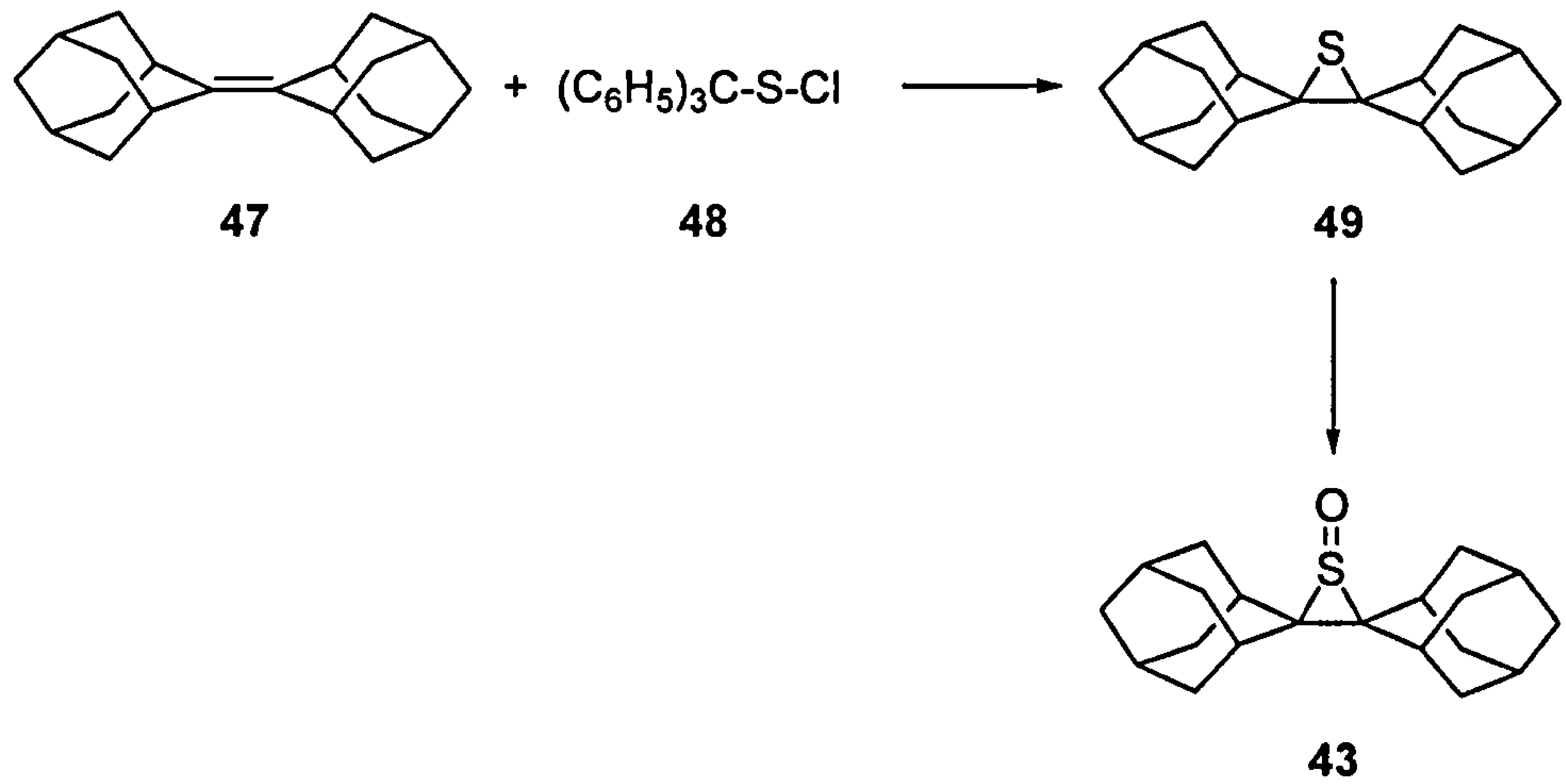
43; n=1
44; n=0

13; R^1, R^2=Me
14; R^1, R^2=Ph
32; R^1=Me, R^2=H
46; R^1=$(CH_2)_2CH$=$C(CH_3)_2$, R^2=H

Scheme 2.12

The reaction proceeded in a variety of solvents at temperatures above 110 °C. Yields were comparable whether the reaction was conducted with equimolar quantities of episulfoxide and diene, an excess of diene or an excess of episulfoxides, the latter combination being slightly superior. Using **43**, the best results were achieved in refluxing toluene, with yields varying from 65% (**46**) to 80% (**13**). Reaction times varied between 12 (**13**) and 36 hours (**32**).

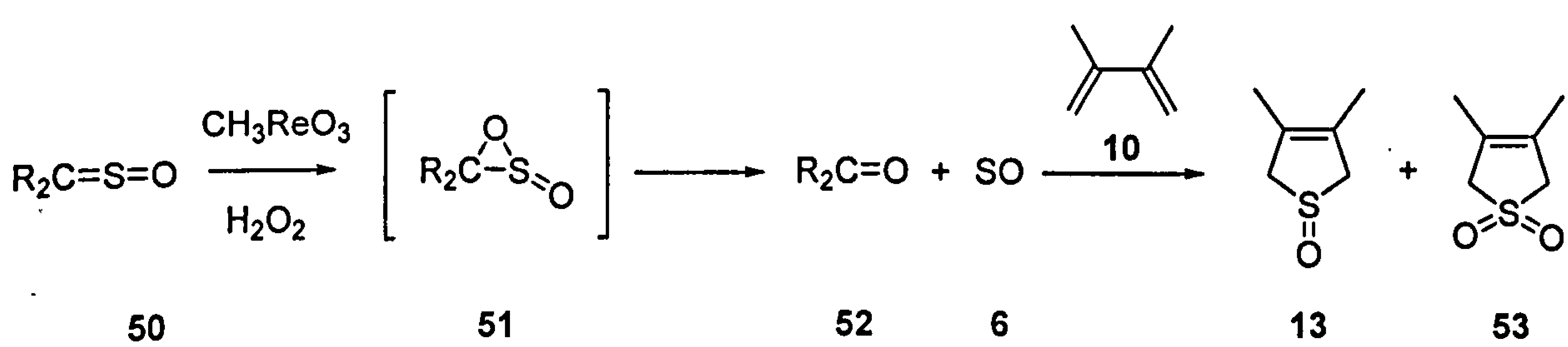
Although proving to be the most efficient and effective SO transfer molecules to date, **43** and **44** are not entirely satisfactory due to their somewhat lengthy preparation. Compound **43** was obtained from the corresponding episulfides **49**; the latter in turn was synthesised by reacting adamantylideneadamantane **47** and triphenylmethanesulfenyl chloride **48**, neither of which is commercially available (Scheme 2.13).



Scheme 2.13

Attempted trapping of diatomic sulfur S_2 with diene **10** by thermal decomposition of **49** met with failure. The only observed products were olefin **47** and elemental sulfur. This, the authors suggested, speaks for a concatenation mechanism of sulfur loss from episulfide **49**.[28] Also, by citing the work by Lemal[17], Baldwin[18] and Glass[19], Harpp acknowledged an SO trapping mechanism going via a biradical intermediate.

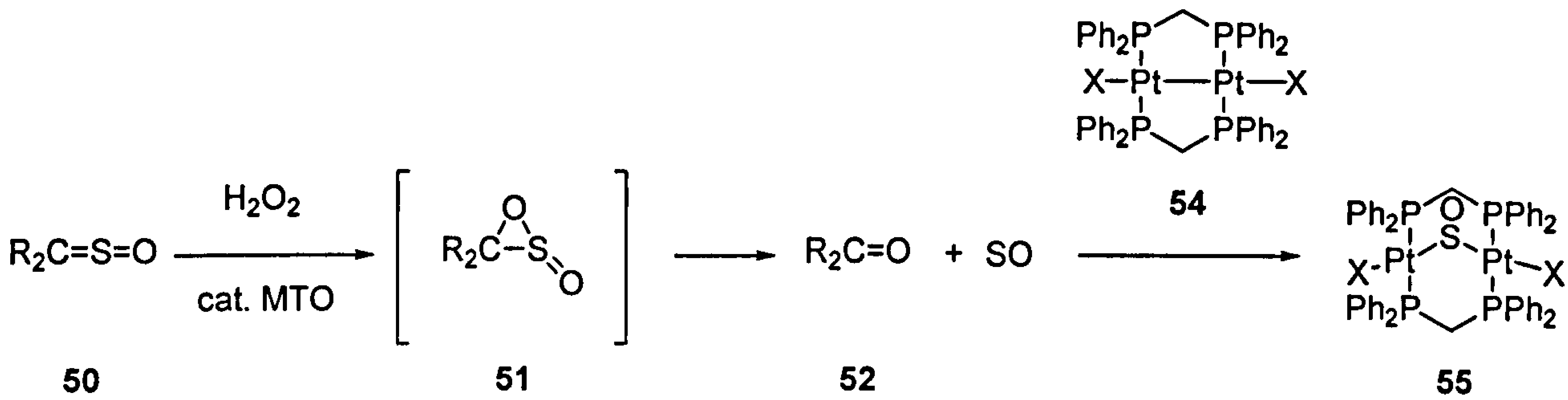
More recently Espenson[29] reported the formation of SO as a decomposition product of sultine intermediate **51**, formed during the H_2O_2 oxidation of thioketones **50** in the presence of catalytic CH_3ReO_3. Standard reaction with 2,3-dimethyl-1,3-butadiene was carried out and the sulfur monoxide was reported to be trapped with 100% efficiency (Scheme 2.14).



Scheme 2.14

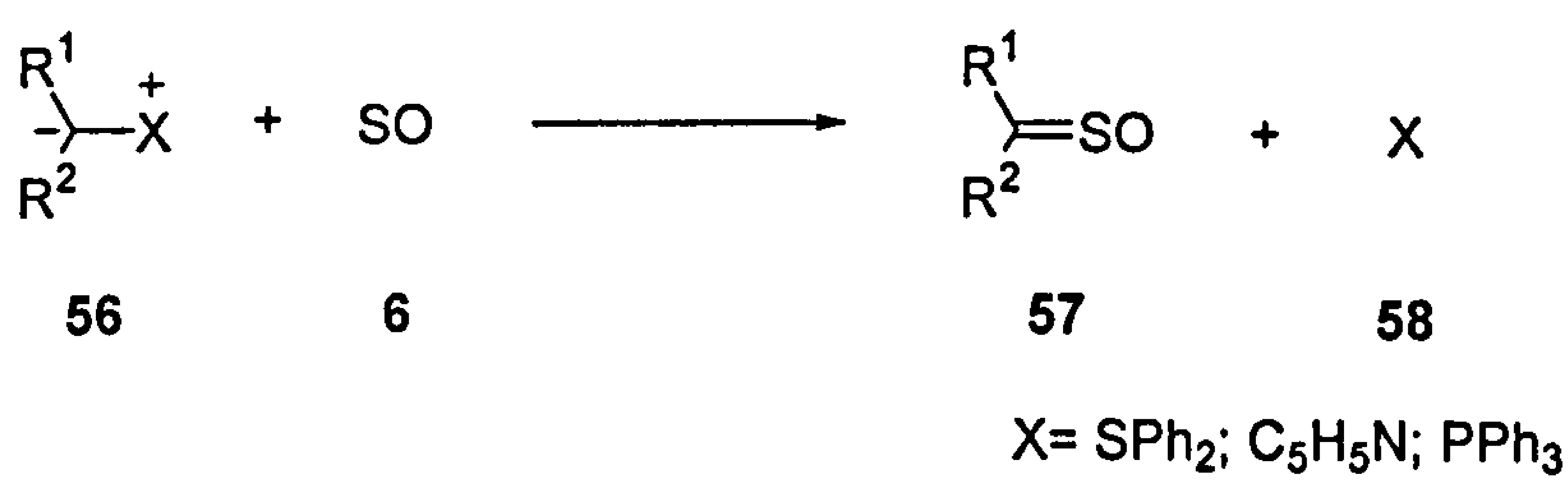
However the strong oxidizing conditions led to formation of sulfone **53** (60 %). Moreover the diene **10** was also subject to oxidation. As a result, yields based on **10** were never higher than 10%.

Later the authors exploited the same methodology to generate structurally interesting platinum complexes **55** of the so-called A-frame $Pt_2(\mu\text{-dppm})_2$ (μ-SO) X_2 family (X= Cl, I, Scheme 2.15).[30]



Scheme 2.15

Free SO is synthetically useful not exclusively in trapping reactions with dienes. A series of papers published by Maccagni and co-workers demonstrated the versatility of this reagent when generated by thermal decomposition of *trans*-2,3-diphenyl thiirane S-oxide. Reactions with potential anionic centers of thermally labile species such as diazoalkanes[31] and arylazides[32] gave thione S-oxides (sulphines) and arylsulphinylamines, respectively. Moreover SO reacts with highly nucleophilic atoms bonded to a good leaving group, such as phosphonium, sulfonium and pyridinium ylides **56**, to furnish thione S-oxides **57**, although in poor yields (11-55%) (Scheme 2.16).[33]



Scheme 2.16

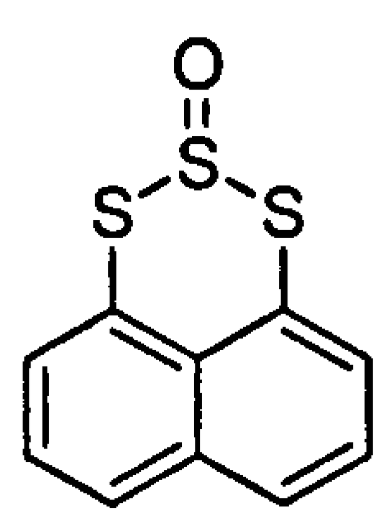
The nature of the R groups was important in dictating reactivity. The best yields were achieved with the most nucleophilic carbanions (R^1 and R^2 = Ph), whereas stable ylides with powerful electron-withdrawing groups (R^1 and R^2 = $PhSO_2$) did not react at all.

AIMS AND OBJECTIVES

2.2.1. Design of a Novel Trisulfide Oxide.

If similarities can be pointed out in the SO-transfer systems developed to date, relief of ring strain seems to be a common driving force for the release of SO. In Dodson, Chow, Harpp and Espenson's cases the SO moiety is "buried" in a three member ring. The inherent tension of these molecules is most likely released by ring opening.[16] The resulting intermediate, whether the mechanism is radical or ionic, is highly reactive and initiates the construction of the less strained five-membered ring.

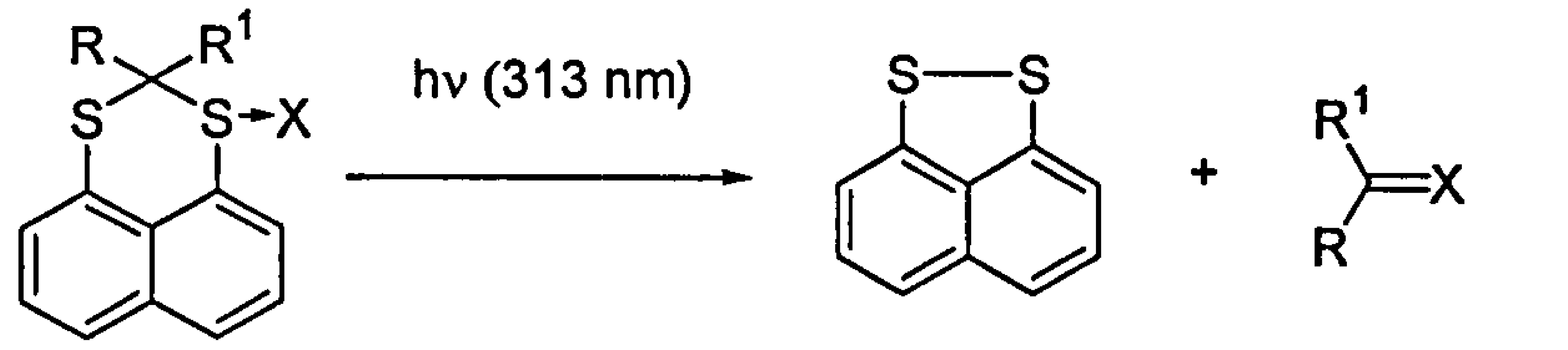
As previously argued (Chapter 1, Paragraph 1.2), "peri" interactions in naphthalene systems provide an ideal platform to construct a strained molecule.[34] Transannular interactions between chalcogen atoms at the 1,8-positions have been exploited as the driving force for reactions in which the tension is ultimately liberated by S-S or Se-Se bond formation.[35] With this knowledge in mind, we envisaged that trisulfide oxide **59** could be a suitable candidate for the generation of sulfur monoxide (Figure 2.2).[36]



59

Figure 2.2

In the literature there was also precedent to suggest that decomposition could be triggered not only thermally but also photochemically. In particular, work by Furukawa demonstrated that photochemical rearrangement of 2- and 2,2-disubstituted naphtho[1,8-*de*]-1,3,dithiin derivatives **60** afforded imine derivatives, olefins, aldehydes and ketones **62** in almost quantitative yields (>99%), along with recovery of disulfide **61** (>99%) (Scheme 2.17).[37]



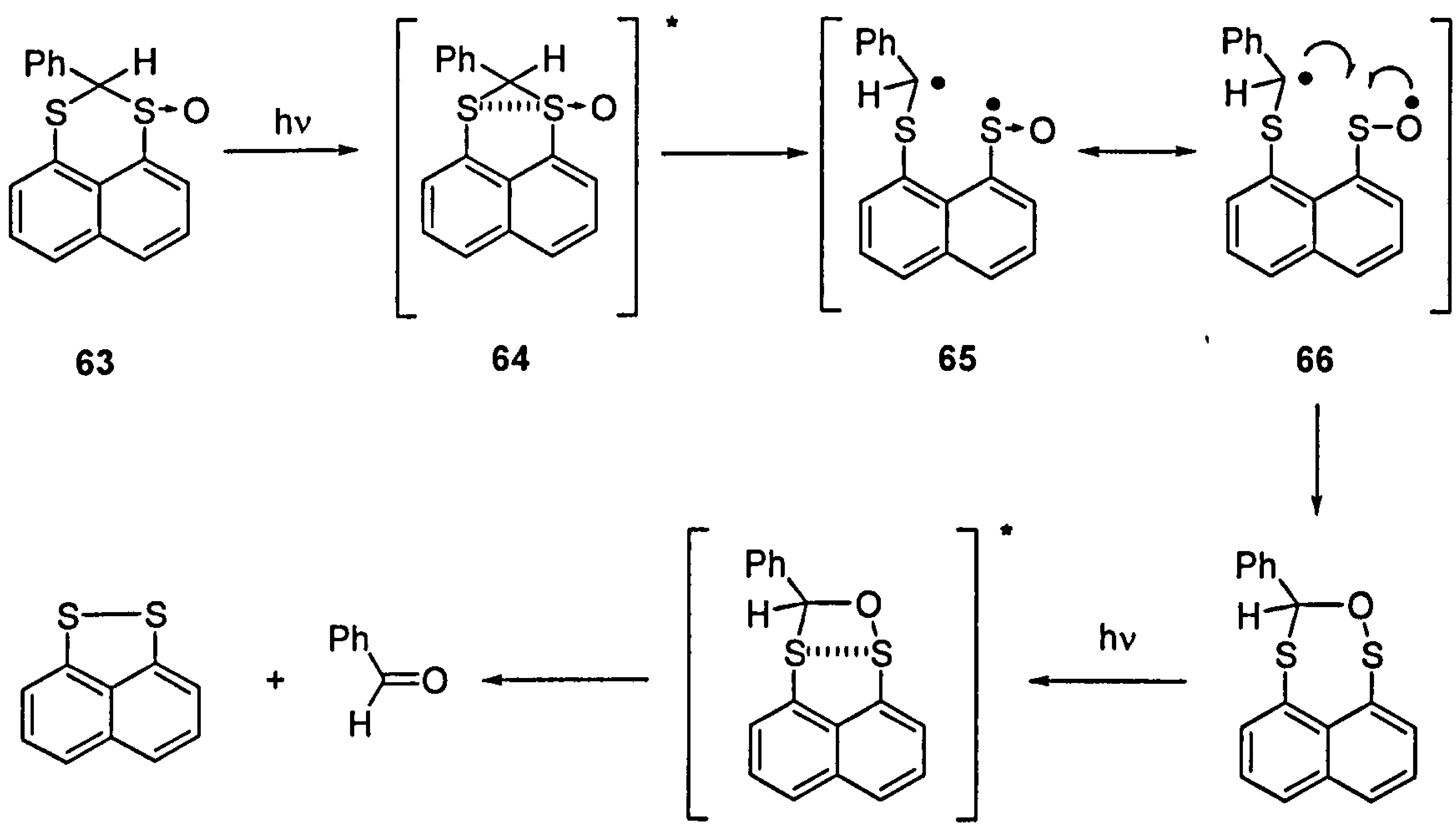
X= O, NTs, $^{-}C(CO_2Et)_2$

R= Ph, $CH_3(CH_2)_5$, PhCH=CH
R^1= H, CH_3, Py, PhCH(OH)-

60 61 62

Scheme 2.17

For the specific case of the sulfoxides **63**, the proposed reaction mechanism goes via the formation of a sulfenic ester **67** in an excited singlet state, in a one electron process (Scheme 2.18).[38]



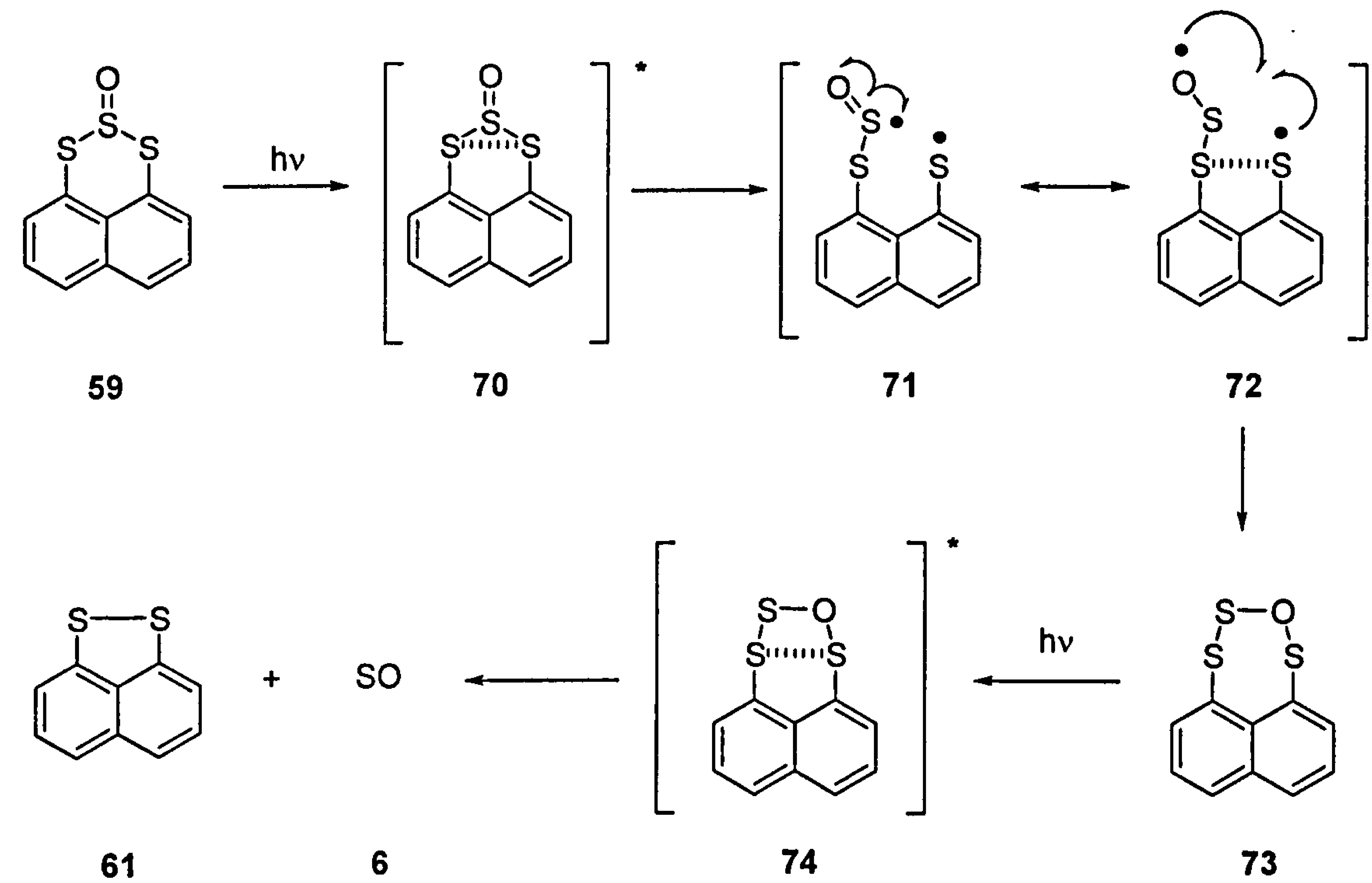
63 64 65 66

61 69 68 67

Scheme 2.18

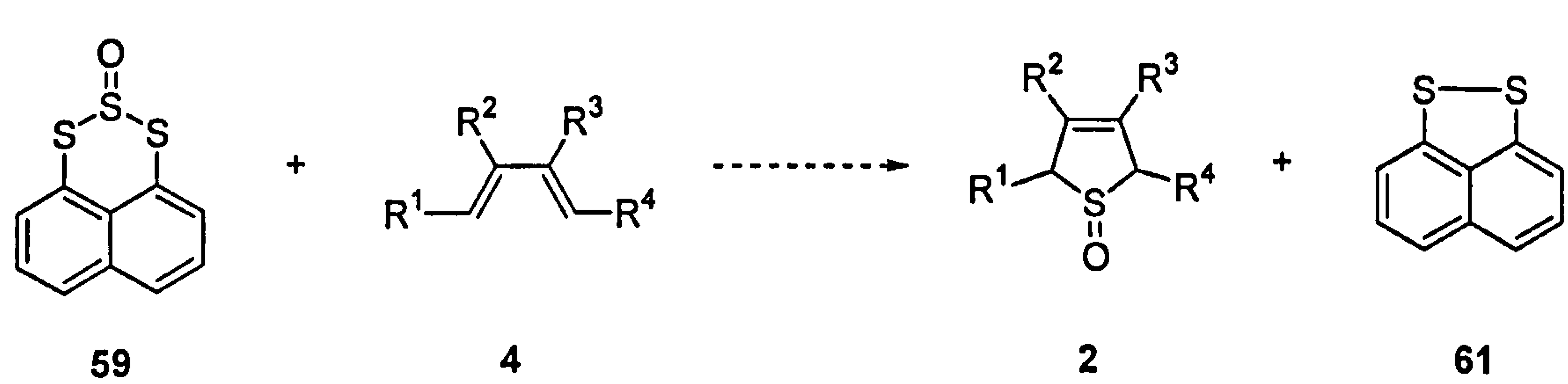
It is well known that many photochemical reactions of sulfoxides proceed via initial formation of sulfenic esters as intermediates.[39] Several sulfenic esters were isolated after photolysis of cyclic sulfoxides.[40] It is hypothesized that the photo-rearrangement of **63** to **67** may be caused by a through-space interaction between the two sulfur atoms in the ground **63** or excited state **64**. In the secondary photochemical step, sulfenic ester **67** undergoes photodecomposition, giving the corresponding disulfide **61** and aldehyde **69**.

Applying the same rationale to **59**, homolytic fragmentation of the S-S bond and rearrangement in the similar fashion as **63** should furnish thioether **73**, which in the secondary photochemical step should decompose to disulfide **61** and SO (Scheme 2.19).



Scheme 2.19

Whether Furukawa[37] or Weiner's[40] rationale would apply, we foresaw that photodecomposition of **59** carried out in the presence of 1,3-dienes **4** should permit trapping of the diatomic molecule and formation of the 1,4-dihydrothiophene S-oxides **2** (Scheme 2.20).

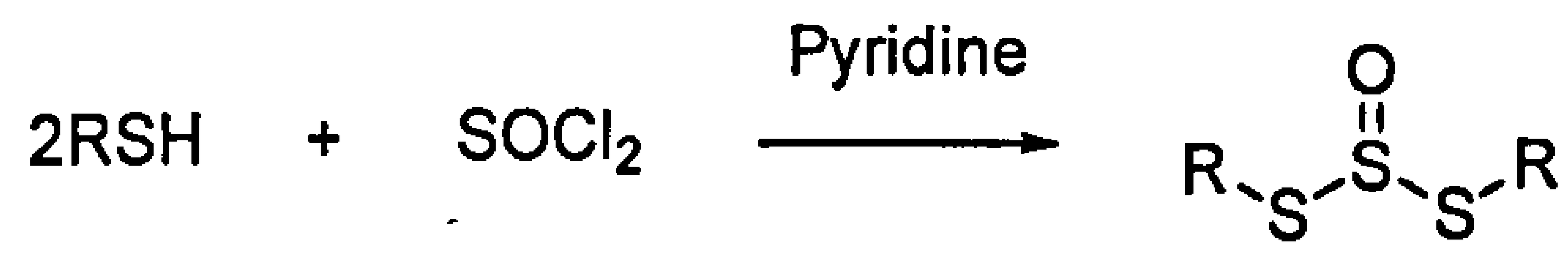


Scheme 2.20

RESULTS AND DISCUSSION

2.3.1. Retrosynthetic Analysis of Trisulfide Oxide.

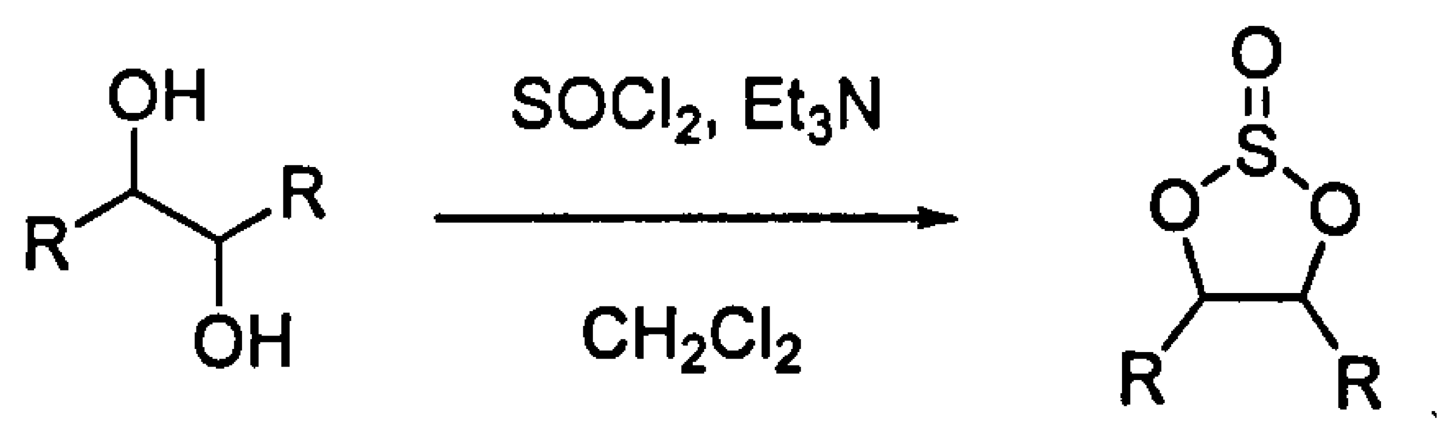
Our synthetic route to **59** was inspired by the work of Lacefield who prepared acyclic dithiosulfites **77** from thiols (Scheme 2.21).[41]



75 **76** **77**

Scheme 2.21

Sharpless prepared cyclic sulfites of the type **79** by treatment of vicinal diols with thionyl chloride in the presence of a base (Scheme 2.22).[42]

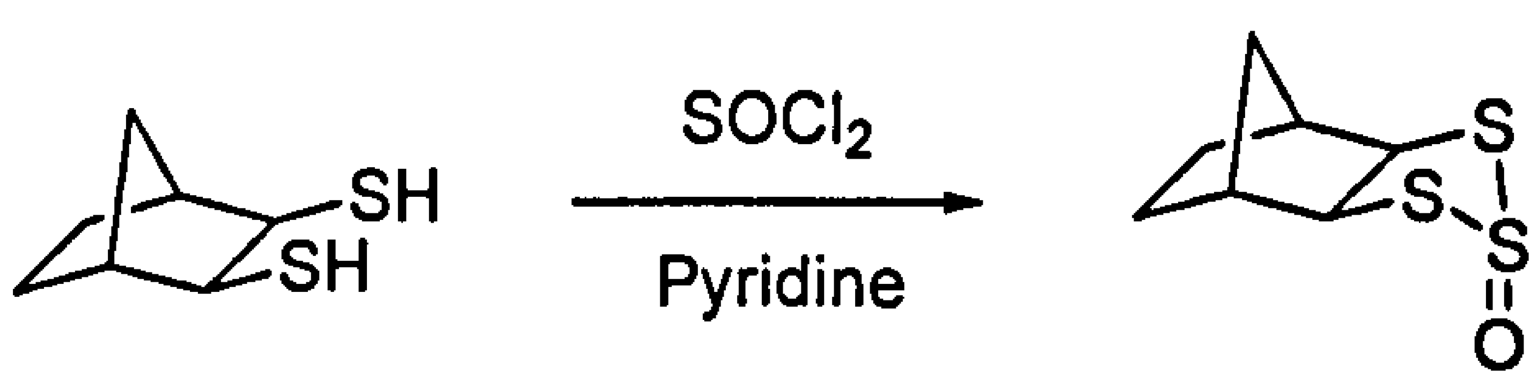


78 **79**

Scheme 2.22

Later, he reported the same reaction just by heating at reflux the diol **78** and thionyl chloride in carbon tetrachloride, in the absence of base.[43]

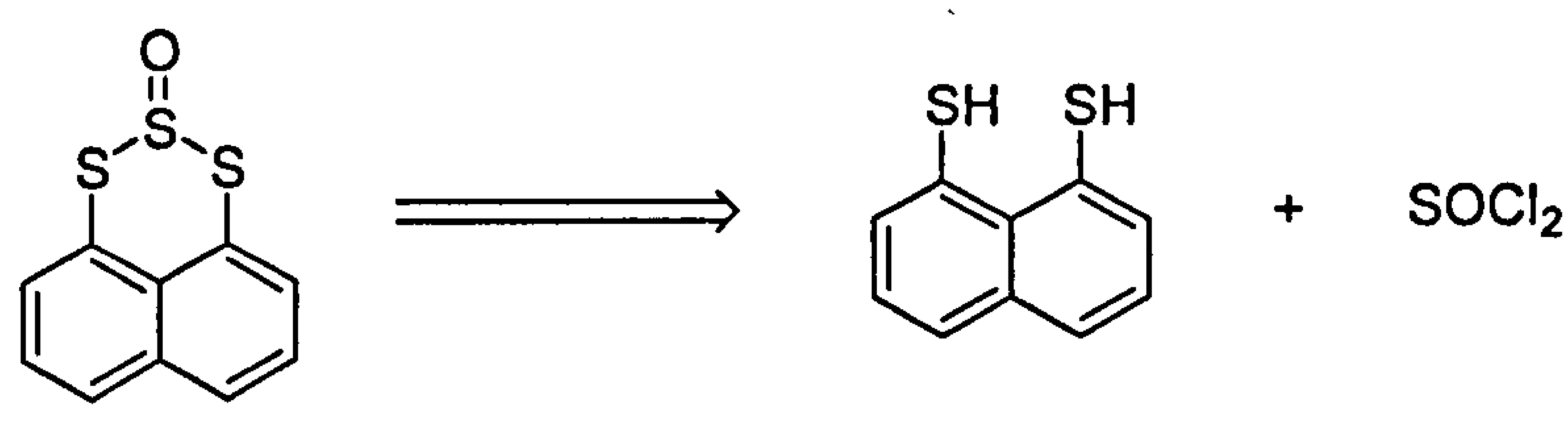
Using a similar procedure, Bartlett reported the preparation of cyclic trisulfide 2-oxide **81** (Scheme 2.23).[44]



80 **81**

Scheme 2.23

We envisaged a general approach to **59** through the coupling of dithiol **82** and thionyl chloride **76** (Scheme 2.24).



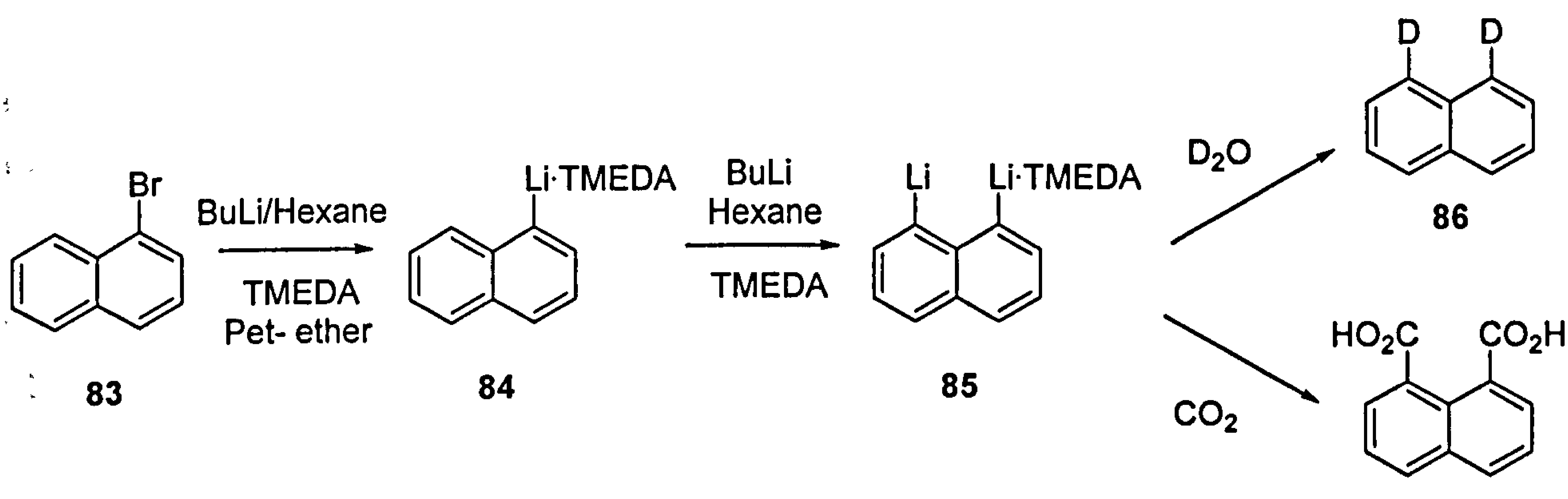
59 82 76

Scheme 2.24

2.3.2. Synthesis of [1,8-c,d]-1,2-Dithiole.

Dithiol **82** can be readily obtained by reduction of the known [1,8-c,d]-1,2-Dithiole **61**, which we had already synthesized (see Chapter 1, Paragraph 1.3.1).[45] However, since **61** was required in large amounts, we felt that the route we had adopted was somewhat inadequate and definitely too lengthy.

We also noted a publication in which a 1,8-dilithionaphthalene species **85** was generated.[46] Quenching with deuterated water or CO_2 yielded **86** and **87** respectively (Scheme 2.25). Detailed yields were not reported, yet **87** was said to be obtained in 86% yield.



(71%)

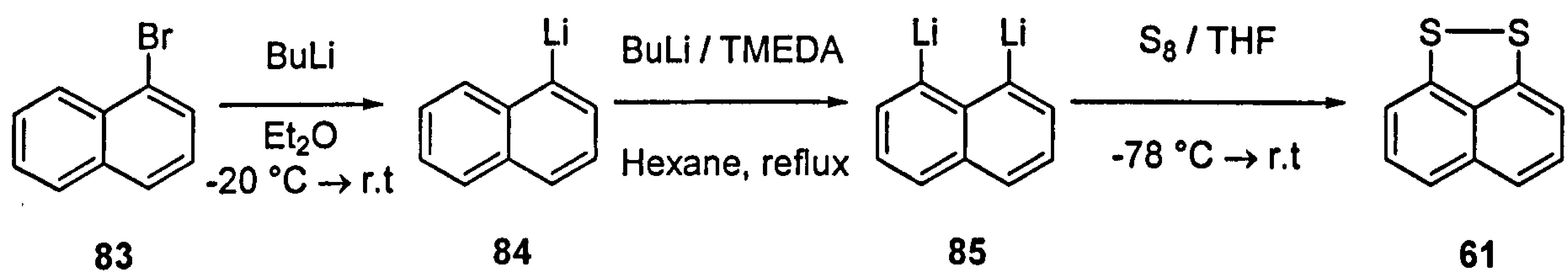
Scheme 2.25

We adopted the same methodology, hoping that upon quenching with sulfur the reaction would furnish **61**.[47] Although the original Neugebauer conditions met with failure, an improved procedure, largely based on the same rationale as that outlined in Scheme 2.25, except for the absence of TMEDA in the lithium-halogen exchange, gave more encouraging results.[48] Refluxing **84** for 3 hours and quenching with a suspension of elemental sulfur in hexane (two equivalents calculated as 8 "S" for every molecule of S_8) at -20 °C furnished the target compound **61** in a 8% yield as a crystalline orange compound. Attempts to purify intermediate **84** by filtration on a sintered funnel, as suggested in the Brandsma paper, led to its decomposition. Also carrying out the second lithiation at room temperature rather than at reflux proved fruitless.

In order to quantify the formation of intermediate **85** we performed the reaction in the same manner as we did when we obtained an 8% yield of **61**, quenching with deuterated water instead of S_8. Here we obtained compound **86** in a 36% yield, comparable with the literature value. This result suggested that the quenching phase was the element we had to turn our attention to. We also hoped that a different allotropic form of sulfur might deliver better results. Repetition of the reaction and final addition of a solution in toluene of S_6 (prepared *in situ*) at room temperature met with failure and no **61** was isolated.

An improvement was achieved when we decided to remove the hexane in which heating for the second lithiation was carried out. Dry **85** was diluted in THF and two equivalents of S_8 were added at -30 °C; the reaction was allowed to reach room temperature and stirred overnight and gave **61** in 17% yield. By further lowering the quenching temperature to -78 °C we improved the yield to 28%. This procedure was subsequently repeated many times giving good results, albeit the yields tended to fluctuate (20-31%). The use of more equivalents of sulfur gave no evident advantage, whereas the use of only one equivalent (per Li) was disadvantageous. Moreover, attempt to quench **85** with another source of electrophilic sulfur (sulfur monochloride) failed, giving no reaction at all.

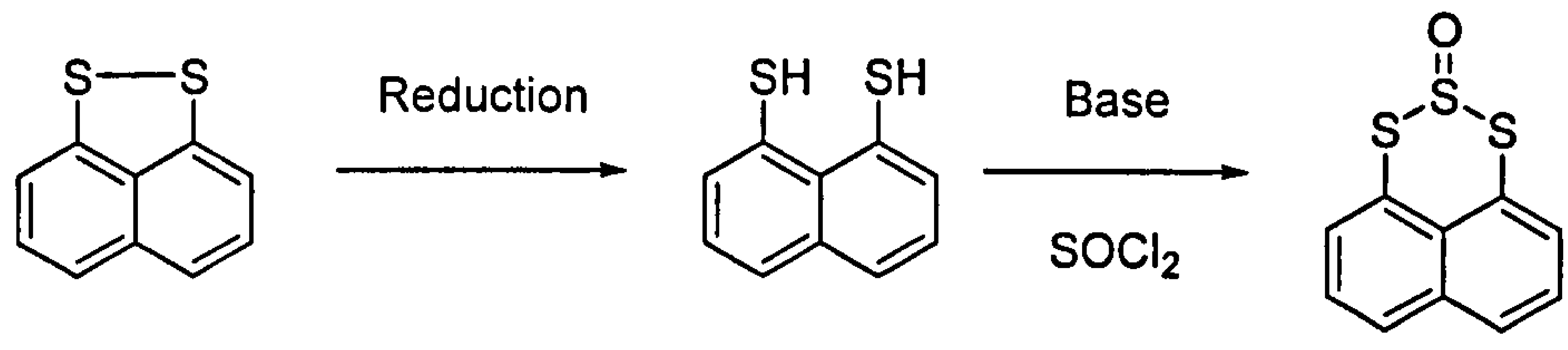
Overall we settled for the following procedure, which equipped us with a way to synthesize **61** on a multigram scale in a multi-step, one-pot reaction (Scheme 2.26).



Scheme 2.26

2.3.3 Synthesis of 1,2,3-Trithia-phenalene 2-oxide.

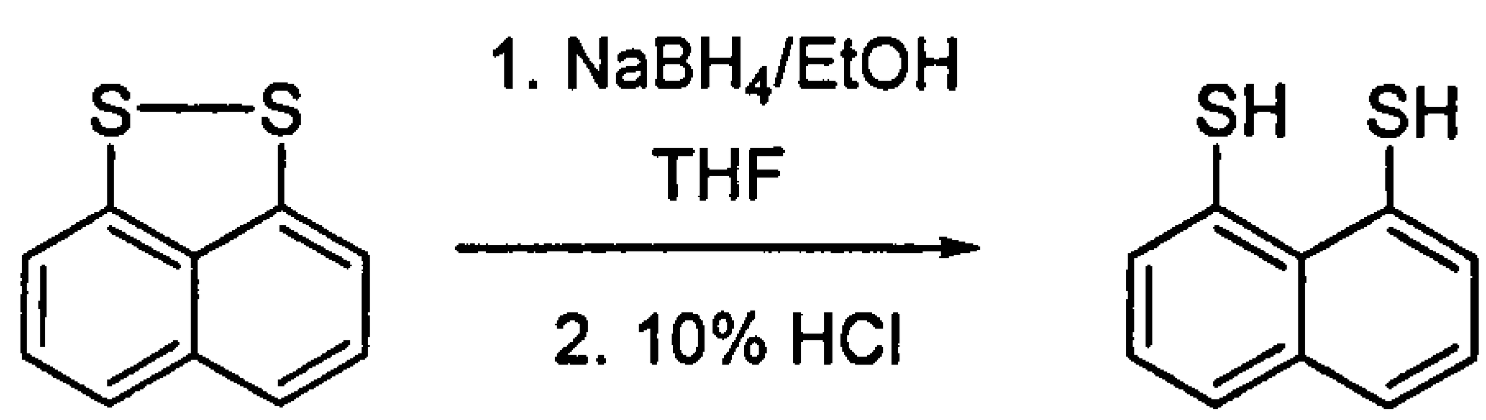
We then went on to couple **82** with thionyl chloride, as outlined in Scheme 2.27.



61 **82** **59**

Scheme 2.27

The reagent of choice for the reduction step was sodium borohydride (suspension in ethanol);[49] to this, a solution of **61** in THF was added. The reaction proceeded at room temperature and after quenching with 10% hydrochloric acid, furnished **82** as a white crystalline solid in quantitative yield (>99%) (Scheme 2.28).

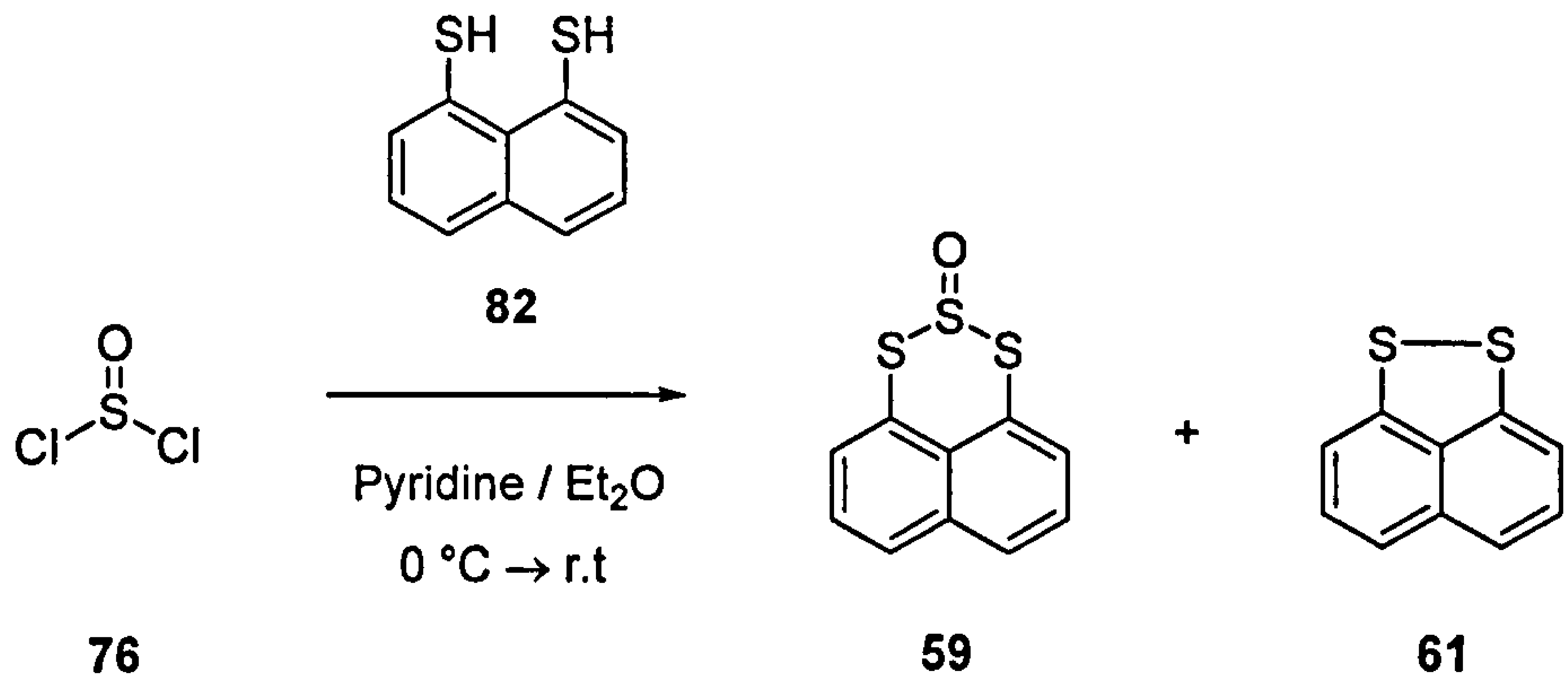


61 **82**

Scheme 2.28

This dithiol could not be stored for long periods, having the strong tendency to oxidize back to **61**. For the same reason it could not be purified by column chromatography. Its purity nevertheless was high enough for our purposes.

For the second step, we initially adopted Bartlett's conditions, his target molecule being most similar to ours (Scheme 2.23). Indeed, addition of a 1:1 mixture of dithiol **82** and pyridine in diethyl ether to a solution of thionyl chloride (1.4 eq.) in diethyl ether gave 1,2,3-trithia-phenalene 2-oxide **59** in 22% yield. The addition was carried out at 0 °C and the reaction was stirred overnight at room temperature; we also recovered 55% of disulfide **61** (Scheme 2.29).



Scheme 2.29

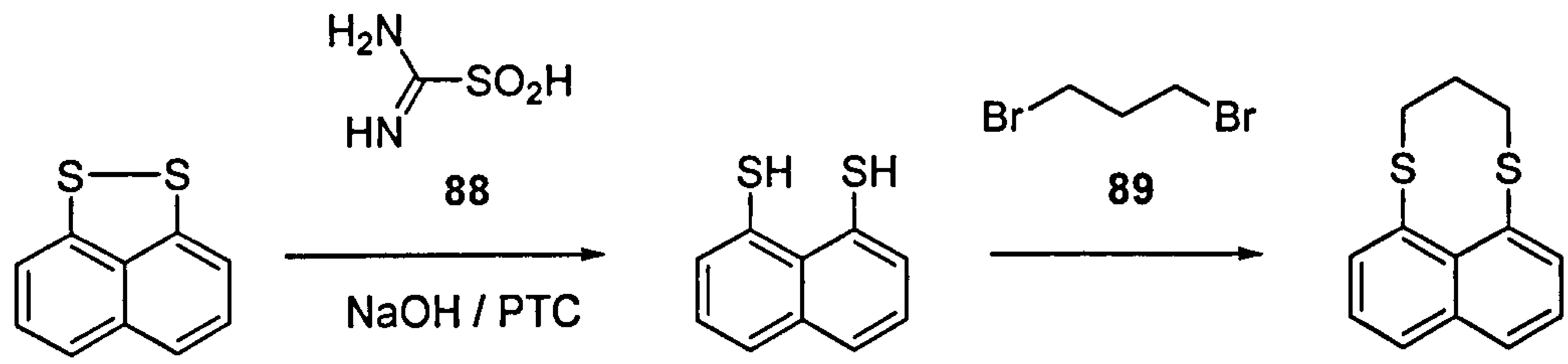
Adopting the same conditions and stirring for two days only afforded disulfide **61**. The same procedure using a solution of thionyl chloride in dichloromethane met with failure.

Shortening the reaction time greatly improved the yield. Work-up and column chromatography after one hour of reaction yielded **59** in 48% yield, along with 50 % of **61**. Slow addition of the mixture and extending the reaction time to three hours did not seem to have a major impact on the outcome. The use of a larger excess (2 equivalents) of thionyl chloride or an equimolar quantity of thionyl chloride:pyridine depleted the yield.

Much more crucial was the handling of dithiol **82**. As already mentioned, it readily oxidizes to the disulfide. Working under a cap of argon while performing the work-up permitted an improvement of the yield to up to 55%, disulfide accounting for the remaining product. Also, extreme care has to be taken in the work-up to remove all traces of water, this being extremely reactive with thionyl chloride. For the same reason, freshly distilled solvents and pyridine gave better results.

Changing the order of addition was totally unsuccessful. Neither the addition of a mixture of pyridine and thionyl chloride to a cooled solution of dithiol, nor the addition of thionyl chloride to a mixture of pyridine and dithiol gave the desired product. Furthermore, we explored changing the temperature of the addition. Lower temperatures (-40 °C and -20 °C) and higher temperatures (room temperature) proved detrimental.

To avoid exposure of the dithiol **82** to air, we examined an alternative reduction system, adopted by Glass on substrate **61**.[50] In the reaction he reported, reduction was carried out with sulfinic acid **88** in the presence of a phase transfer catalyst; there was no need for the work-up and coupling with 1,3-dibromopropane **89** species was effective (Scheme 2.30).



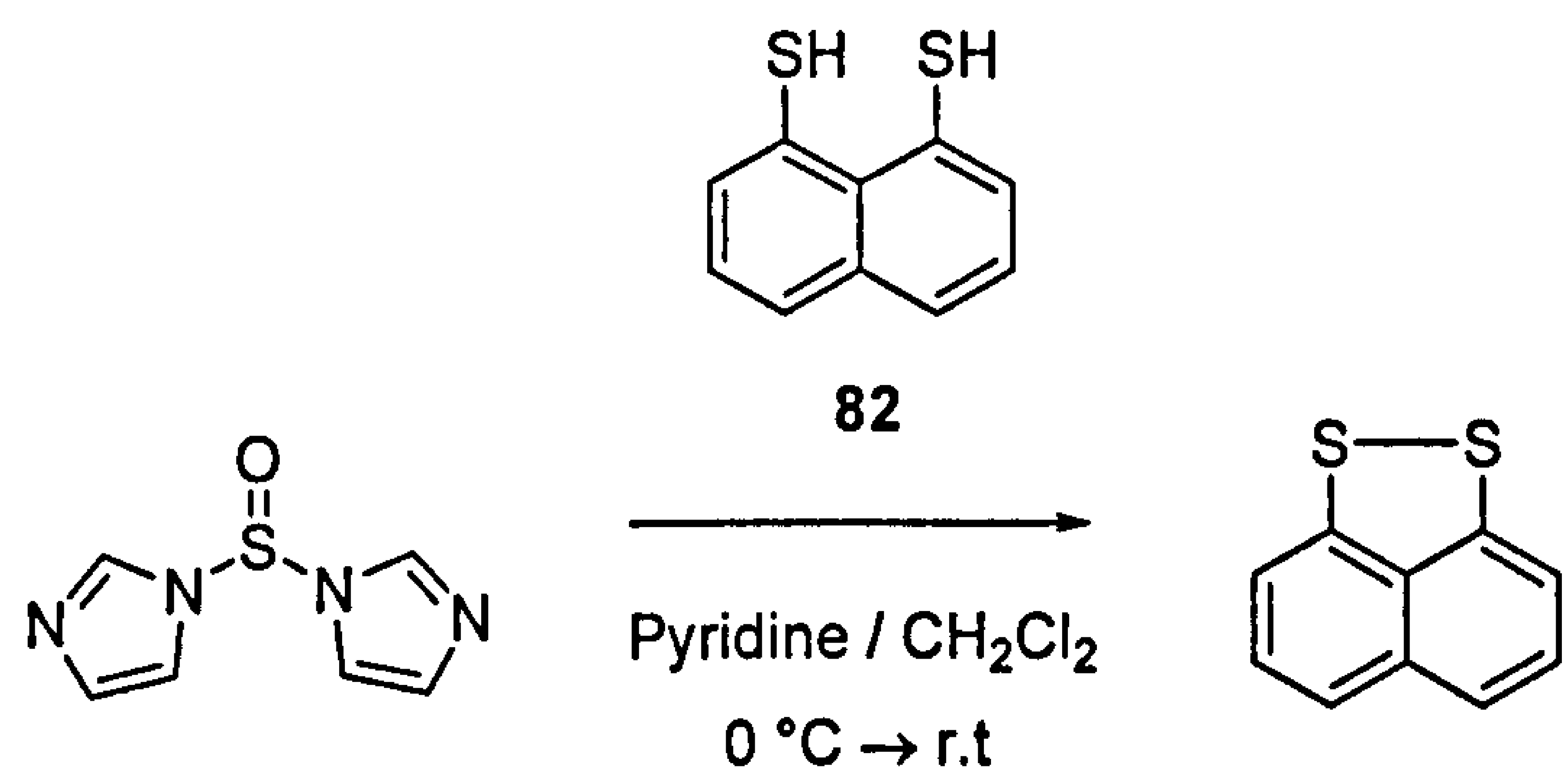
61 82 90

Scheme 2.30

In our hands the substrate underwent reduction (change of color from red to colorless) but *in situ* reaction with thionyl chloride did not take place.

With the same goal in mind we also tried a one-pot reaction in which, after the reduction step, the unreacted sodium borohydride was consumed by adding acetone. Deprotonation was then attempted using potassium hydroxide. Upon addition of thionyl chloride the mixture became dark and no product was observed.

An alternative reagent to thionyl chloride proposed in the literature is 1,1'-thionyldiimidazole **91**,[51] in which the two imidazole units represent alternative leaving groups to the chlorine. The reagent was prepared according to the reported method,[52] which furnished the product as a solution in dichloromethane. Standard reduction was performed on the disulfide and after quenching with 10% HCl, dithiol **82** was extracted with dichloromethane. To this solution was added the 1,1'-thionyldiimidazole solution at 0 °C, only to obtain disulfide **61** (Scheme 2.31). Inverse order of addition gave identical results.



91 61

Scheme 2.31

In spite of all our efforts not to expose dithiol to air, the presence of a mixture of THF, water and ethanol after the acid quench rendered the extraction phase necessarily laborious, especially when working on a large scale. This resulted in partial oxidation of the dithiol by the time this was redissolved in diethyl ether (displayed by darkening of the solution). On the other hand, avoiding the use of ethanol by carrying out the sodium borohydride reduction in pure THF did not succeed.

Lithium aluminium hydride (LAH) has been reported to reduce disulfides to thiols in THF.[45b] Indeed when a solution of **61** was added to a suspension of LAH at room temperature, lightening of the colour suggested that reaction was taking place. Nevertheless to drive the reduction to completion, a large excess of LAH had to be used. Upon quenching with 10% H_2SO_4, a gelatinous mass formed and the work-up turned out to be more time consuming than before. A suggested work-up for LAH reductions[53] that prescribes successive washings with water, 15% NaOH and water again did prove effective in removing the side products; yet it was still too lengthy.

After several attempts we finally tuned a methodology that suited our requirements of efficiency and quickness: LAH was suspended in diethyl ether and a solution of **61** in dry diethyl ether was added and the mixture hated at reflux (15 minutes). The reaction was then quenched with 10% H_2SO_4, washed with brine and quickly extracted twice with dichloromethane. The combined organic layers were dried over $MgSO_4$ and filtered without further washings; the solvent was removed *in vacuo*, with the Rotavapor connected to a reservoir of argon for the pressure equilibration phase (later extractions of the reaction mixture and washings of the filter paper allowed the recovery of the remaining then re-oxidised **61**, normally a minor fraction). The resulting dithiol **82** was dissolved in diethyl ether and pyridine added. This mixture was subsequently added to a solution of thionyl chloride in diethyl ether at 0 °C, to give a mixture of **61** and **59**. This allowed us to increase the yield of **59** up to a maximum of 65%.

X-ray quality crystals were obtained by slow evaporation of a dichloromethane solution of **59** in a hexane atmosphere. The structure obtained highlights a number of interesting structural features (Figure 2.3).

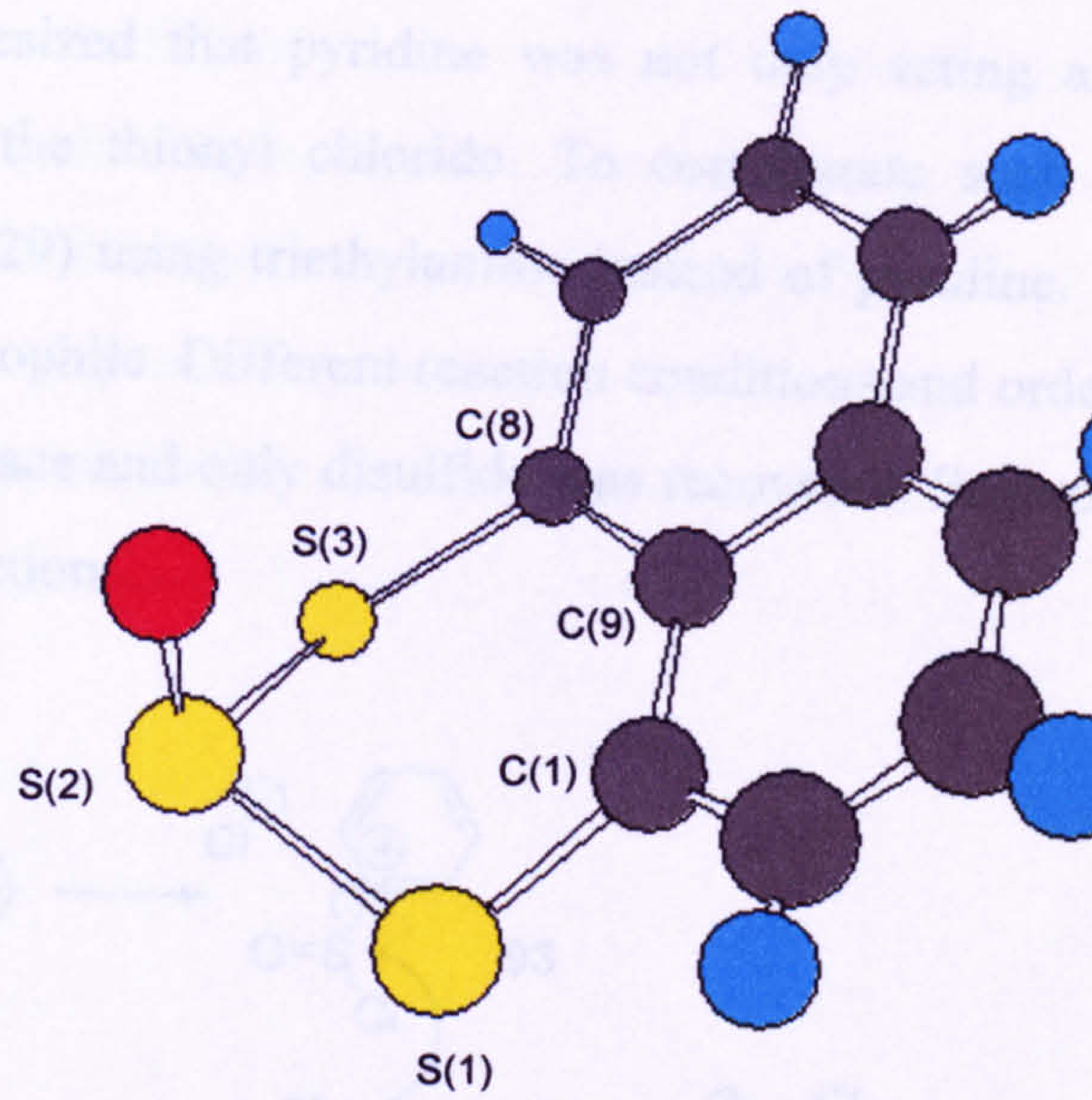


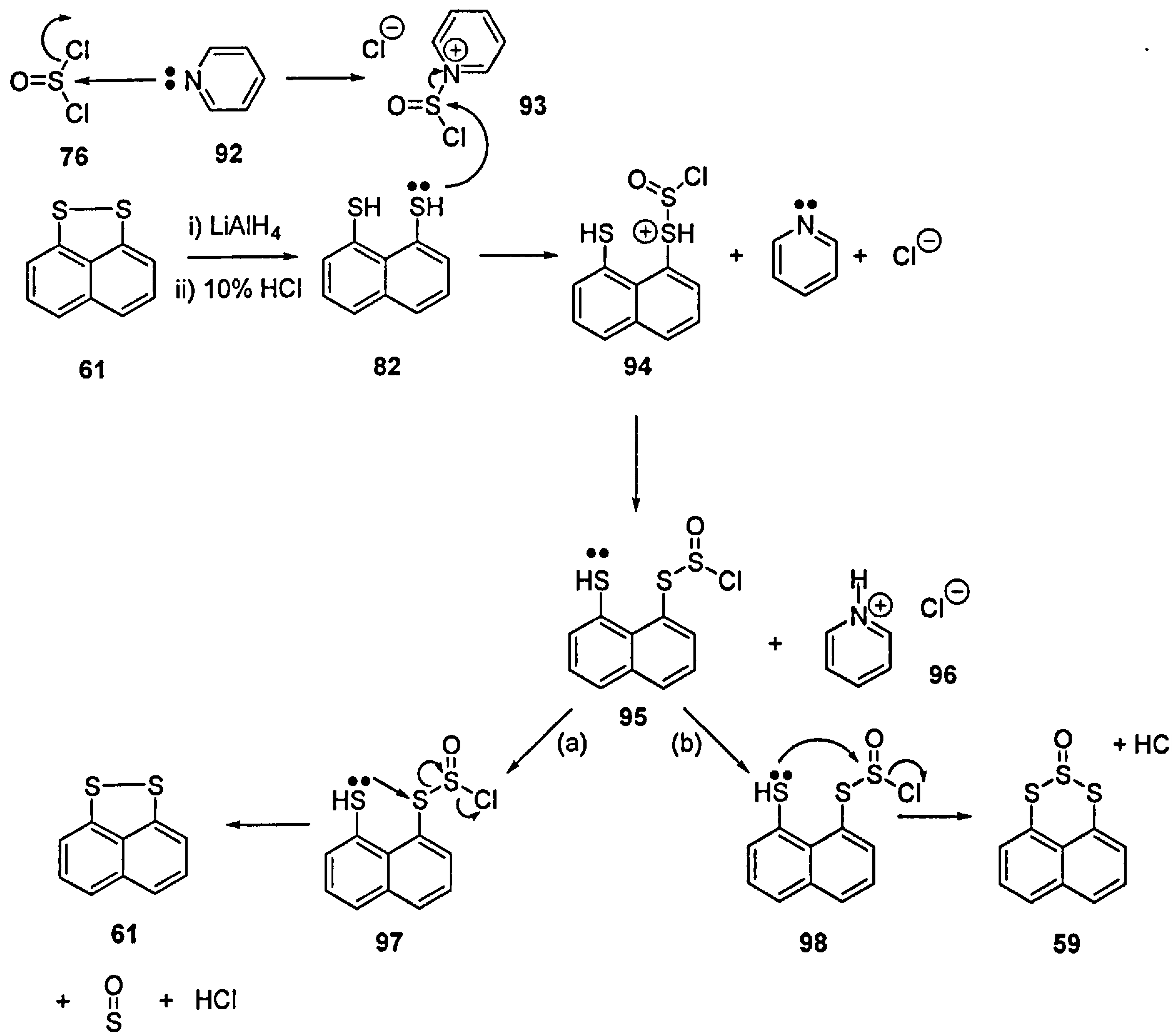
Figure 2.3

A nonplanar conformation is adopted by the trithiane ring, whereby the central sulfur atom S(2) lies out of the mean least-squares plane of the naphthalene ring and *peri*-sulfur atoms by 1.1708(14) Å (torsion angles C1-S1-S2-S3, 60.1 and C8-S3-S2-S1, 64.6, respectively). The oxygen atom occupies a pseudoaxial position on the trithiane ring, probably as a result of stabilization of this conformer through stereoelectronic effects.[54] Pseudoaxial oxygen is also observed in other cyclic trisulfide oxide derivatives for which the X-ray crystal structures are known (all five-membered rings).[55]

Two factors point to the strain in the system. First, the enlargement of the expected bond angles at C(1), C(9), and C(8) (125.7, 126.6, and 124.7) is consistent with the minimization of steric interactions associated with the close proximity of substituents at the 1,8-positions of the naphthalene ring system.[33] Second, whereas S(1) is essentially coplanar with the naphthalene ring, S(3) lies 0.203(4) Å out of the mean least-squares plane, on the opposite side to S(2).

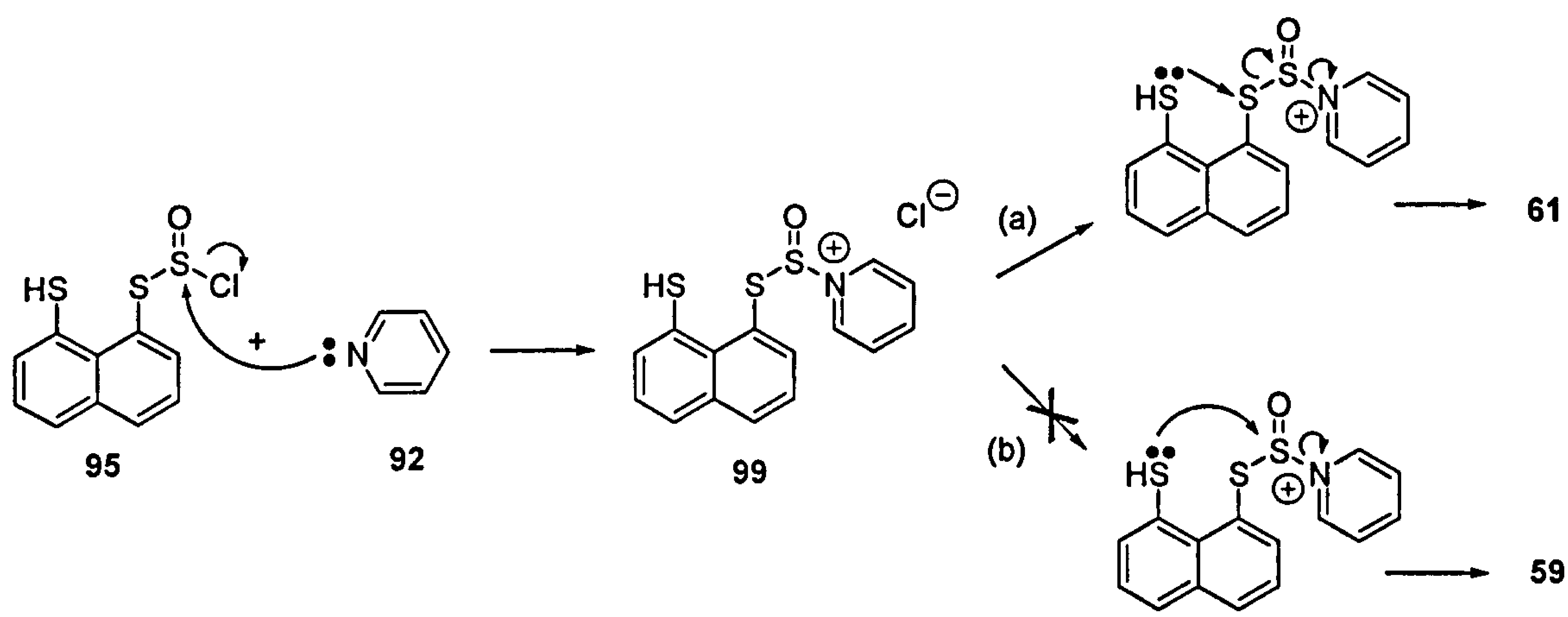
In an extra effort to further increase the yield, we turned our attention to the work of Lacefield (Scheme 2.21). As opposed to Bartlett's procedure, he used pyridine:thiols:thionyl chloride in a (logical) ratio of 2:2:1. Adoption of the same rationale (two moles of pyridine for each mole of dithiol) proved disastrous. Little product was isolate and side products were impossible to characterize. On top of this we were not able to recover quantitatively disulfide **61**. Changing solvents, reaction temperature and the order of addition led to no further progress.

We therefore hypothesized that pyridine was not only acting as a base but also as an activating group for the thionyl chloride. To corroborate such idea we tried the same procedure (Scheme 2.29) using triethylamine instead of pyridine. The former is a stronger base but a worse nucleophile. Different reaction conditions and orders of addition were tried, yet no reaction took place and only disulfide was recovered. Scheme 2.32 depicts a possible mechanism for the reaction.



Scheme 2.32

Upon addition of pyridine to thionyl chloride, 1-chlorosulfinylpyridinium chloride **93** is formed *in situ*. One of the sulfur atoms in **82** attacks **93** to form intermediate **94**; the pyridine so generated deprotonates **94** to form **95** and pyridinium chloride **96**. Indeed formation of an insoluble salt (presumed to be **96**) was observed during the reaction. Intermediate **95** now has two possible reaction pathways. In the first (a), the lone pair on the thiol attacks the adjacent sulfur to give disulfide **61**; in the second (b) it attacks the tetravalent sulfur to give the desired product **59**. In fact both the products were routinely observed. However we cannot discard the possibility that only path (b) effectively takes place and that the disulfide **61** recovered in the every reaction is solely formed by the re-oxidation of dithiol **82**. Working with an excess of pyridine is likely to promote nucleophilic attack on intermediate **95**. The so-formed intermediate **99** may prove too bulky for pathway (b) to prevail (Scheme 2.33).

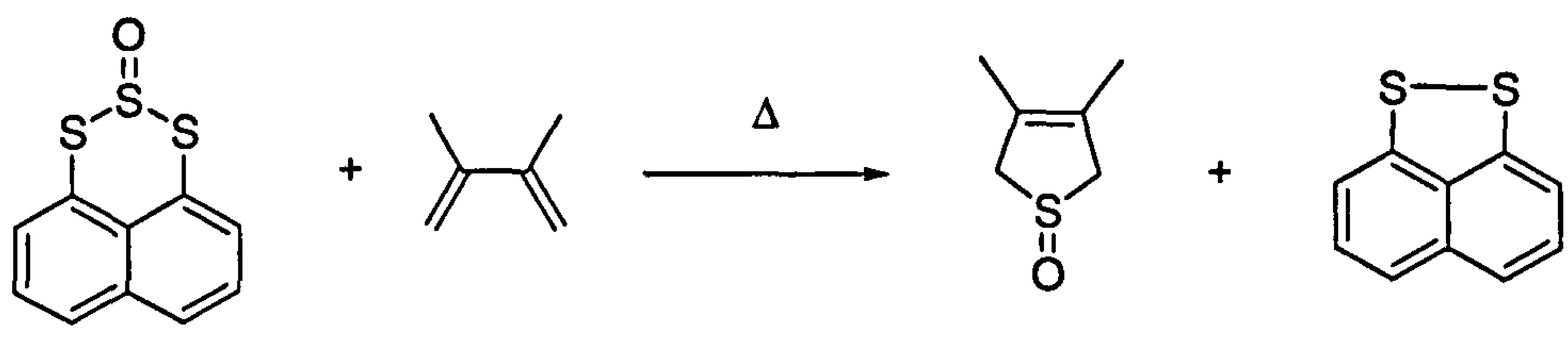


Scheme 2.33

This rationale added credence to the failure we observed when using a reagent such as 1,1-diimidazole sulfoxide **91** (Scheme 2.31). Also, the negative results obtained by pre-mixing thionyl chloride and pyridine or by adding thionyl chloride to the mixture of dithiol and pyridine point to the same conclusion. It seems important to work in conditions where there is an excess of thionyl chloride, to make sure there is no free pyridine once intermediate **95** has formed.

2.3.4. Thermal Trapping Experiments with 1,3-Dienes.

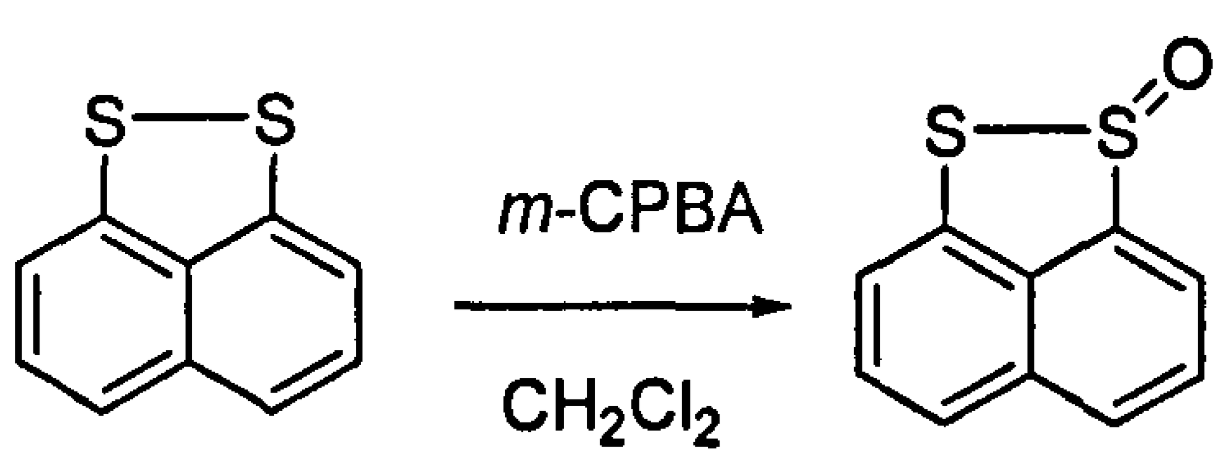
Although the reaction in our hands still behaved somewhat capriciously, we could prepare trisulfide oxide **59** on the gram scale. The outstanding results obtained by Harpp[23] prompted us to first the test thermal behaviour of **59** in the presence of 1,3 dienes. The results are summarized in Table 2.2. Dienes were chosen based on their commercial availability, starting from 2,3-dimethyl-1,3 butadiene (Scheme 2.34), which allowed for direct comparison with Harpp's system.



59 **10** **13** **61**

Scheme 2.34

A mixture of **59** and **10** (1:20) was dissolved in chlorobenzene and stirred overnight at room temperature. No reaction was observed. By heating at reflux the same mixture for 24 hours we were delighted to detect the target molecule **13** (^{1}H NMR). The other observed products were disulfide **61** and a small amount of thiosulphinate **100** (Scheme 2.35). The identity of compound **100** was established by comparison with a pure sample prepared from *m*-CPBA oxidation of **61** (see Chapter 1, Experimental Section - Paragraph 1.4.).

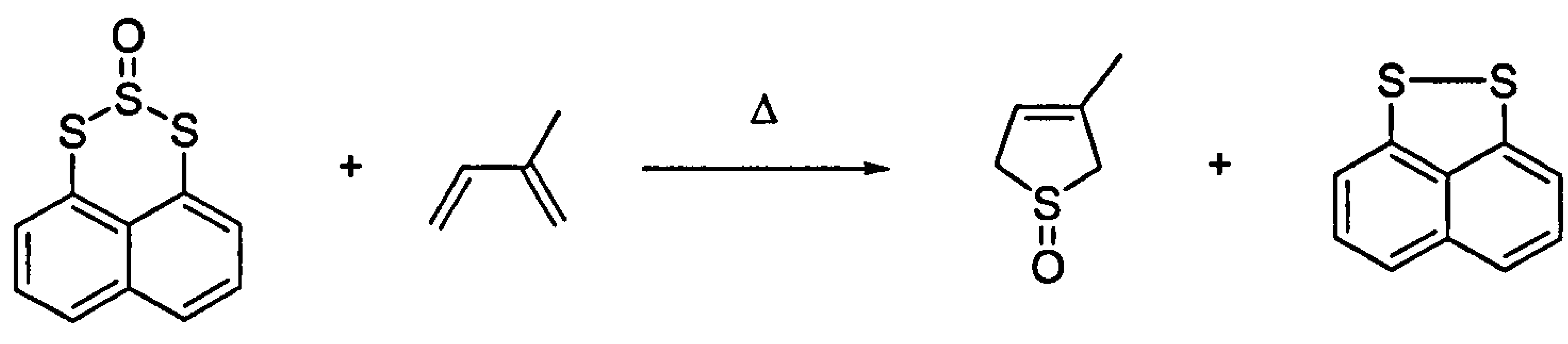


61 **100**

Scheme 2.35

The three products were produced in a ratio of 25:23:3 (**61**: **13**: **100**). The reaction was repeated on a larger scale, taking the precaution of degassing the chlorobenzene solution using argon. After 15 hours reaction and aqueous work-up, purification by column chromatography yielded solely the disulfide **61** (100%) and 2,3-dimethyl-1,4-dihydrothiophene **13** (99%) (Table 2.2, entry 3).

The use of another diene, 2-methyl-1,3-butadiene **30** (isoprene) also gave excellent results (Scheme 2.36).



59 30 32 61

Scheme 2.36

Heating at reflux a mixture of **59** and **30** (1:20) in chlorobenzene for 6 hours gave **32** in 74% yield with a quantitative recovery of **61** (Table 2.2, entry 6). Extending the reaction time to 15 hours decreased the yield to 50% (entry 7). When the experiments in Scheme 2.36 were repeated using non-degassed solvent again we noticed formation of thiosulfinate **100**, albeit in small quantities.

Harpp has reported that cyclic sulfoxides are thermally labile.[22] We therefore attempted the thermal decomposition using solvents with a lower boiling point compared to that of chlorobenzene. Haeting at reflux **59** and **10** (1:3) in $CDCl_3$ for 15 hours led to partial decomposition (10%, based on ^{1}H NMR) of the trisulfide to yield the corresponding disulfide. No other product could be characterized (entry 1). The same reaction was carried out in propionitrile (entry 5). After 17 hours of heating at reflux, TLC analysis showed large quantities of the trisulfide oxide left. The reaction was interrupted after 35 hours and column chromatography furnished unreacted **59**, 35% of the disulfide **61** and traces of **13**. Reaction of **59** and **30** in toluene heating at reflux (bp 110 °C) gave **32** (65%) and 100% of disulfide but it took 26 hours to go to completion (entry 8). We therefore concluded that chlorobenzene (bp 132 °C) was a suitable solvent to carry out the decomposition of **59**.

To confirm this observation, Differential Scanning Calorimetry (DSC) was performed on a pure sample of **59**. Indeed a sharp endothermic peak appeared at 120 °C, with an on-set temperature of around 108-110 °C.

Also Thermal Gravimetric Analysis (TGA) gave consistent results. A weight loss of 13.34% was detected at temperatures around 120 °C. The "SO" fragment accounts for 20.16% of the molecular weight of trisulfide oxide **59**.

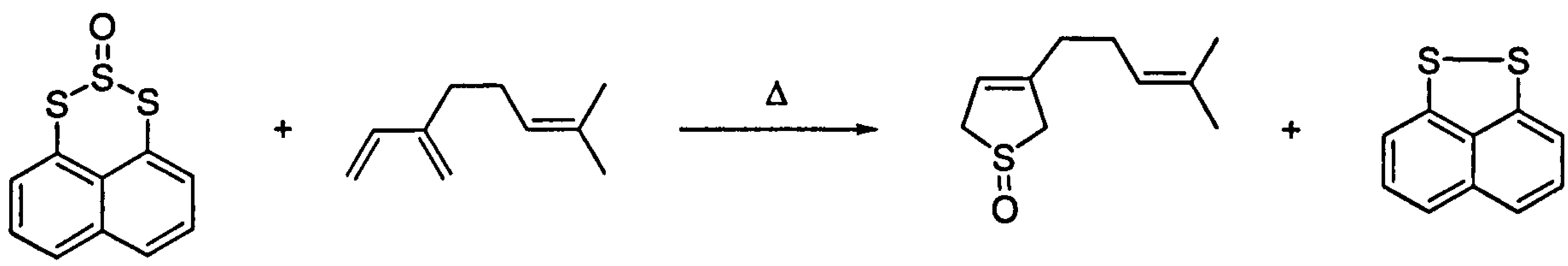
However it is known that SO is extremely unstable and rapidly disproportionates according to Scheme 2.37. Presumably the decomposition process is further accelerated when the molecule is released at high temperature.

$$48\,SO \longrightarrow 8SO_2 + 16S_2O$$
$$16S_2O \longrightarrow 8SO_2 + 8S_3$$
$$8S_3 \longrightarrow 3S_8$$

Scheme 2.37

According to the stoichiometry outlined in Scheme 2.37, only 67% of the released SO remains gaseous (SO_2), whereas the rest is solid (at temperatures between 120 and 150 °C) and should not contribute to weight loss (S_8). As such, only (20.16 times 0.6693 =) 13.5% should be the detected weight loss, which is extremely close to the experimental value.

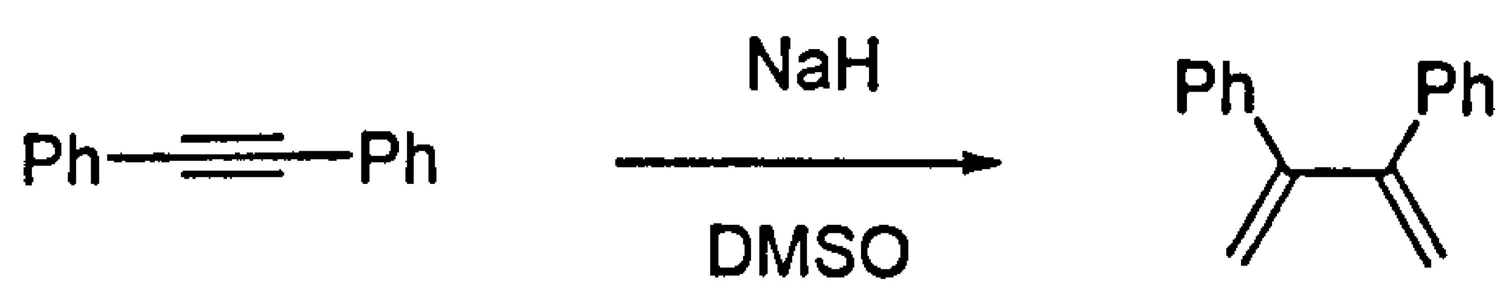
Another commercially available 1,3-diene is myrcene (7-methyl-3-methylene-1,6-octadiene) **45**. A point of interest in this molecule is the presence of the 1,3, 1,6 and 3,6 diene relationships; however thermal decomposition of **59** in refluxing chlorobenzene in the presence of diene **45** yielded only adduct **46**. In spite of using a smaller excess of diene compared to the previous reactions (**59**:**45** 1:2.5), **46** was isolated in 93% yield, along with 100% of **61** (Scheme 2.38) (Table 2, entry 18).



59 **45** **46** **61**

Scheme 2.38

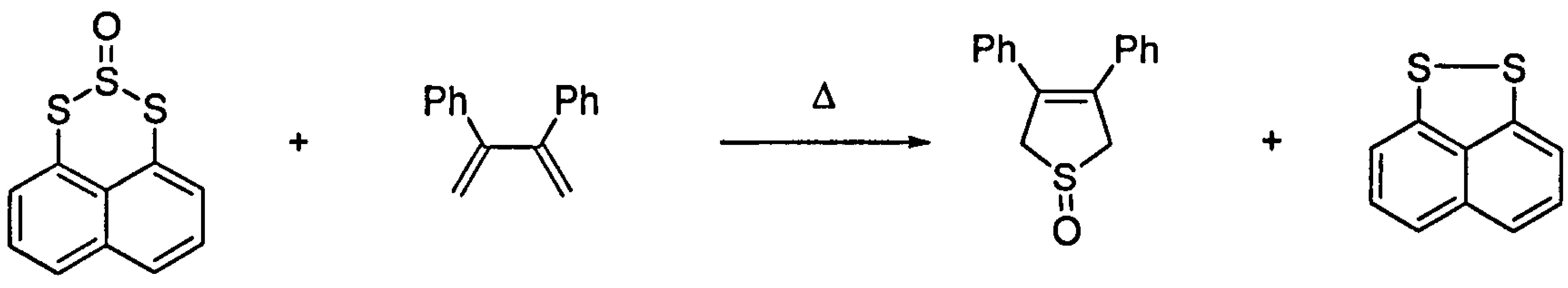
As expected, the reaction in toluene at 80 °C did not proceed (entry 14) and when heated at reflux occured only very slowly. Nevertheless it furnished **46** (71%) after 24 hours (entry 15). In order to complete the comparison with Harpp's system, which is the most effective SO transfer agent to date found in the literature, we attempted to prepare 2,3-diphenyl, 1,3 butadiene according to the reported procedure shown in Scheme 2.39.[56]



101 **11**

Scheme 2.39

The yields however were low (around 10%) and the material obtained was impure; therefore the diene **11** was obtained from a commercial supplier. The trapping reaction was carried under our standard conditions (**59**:**11** 1:2.5) and after 6.5 hours we isolated **14** in 65% yield along with the complete recovery of **61** (Scheme 2.40; Table 2.2, entry 10).



Scheme 2.40

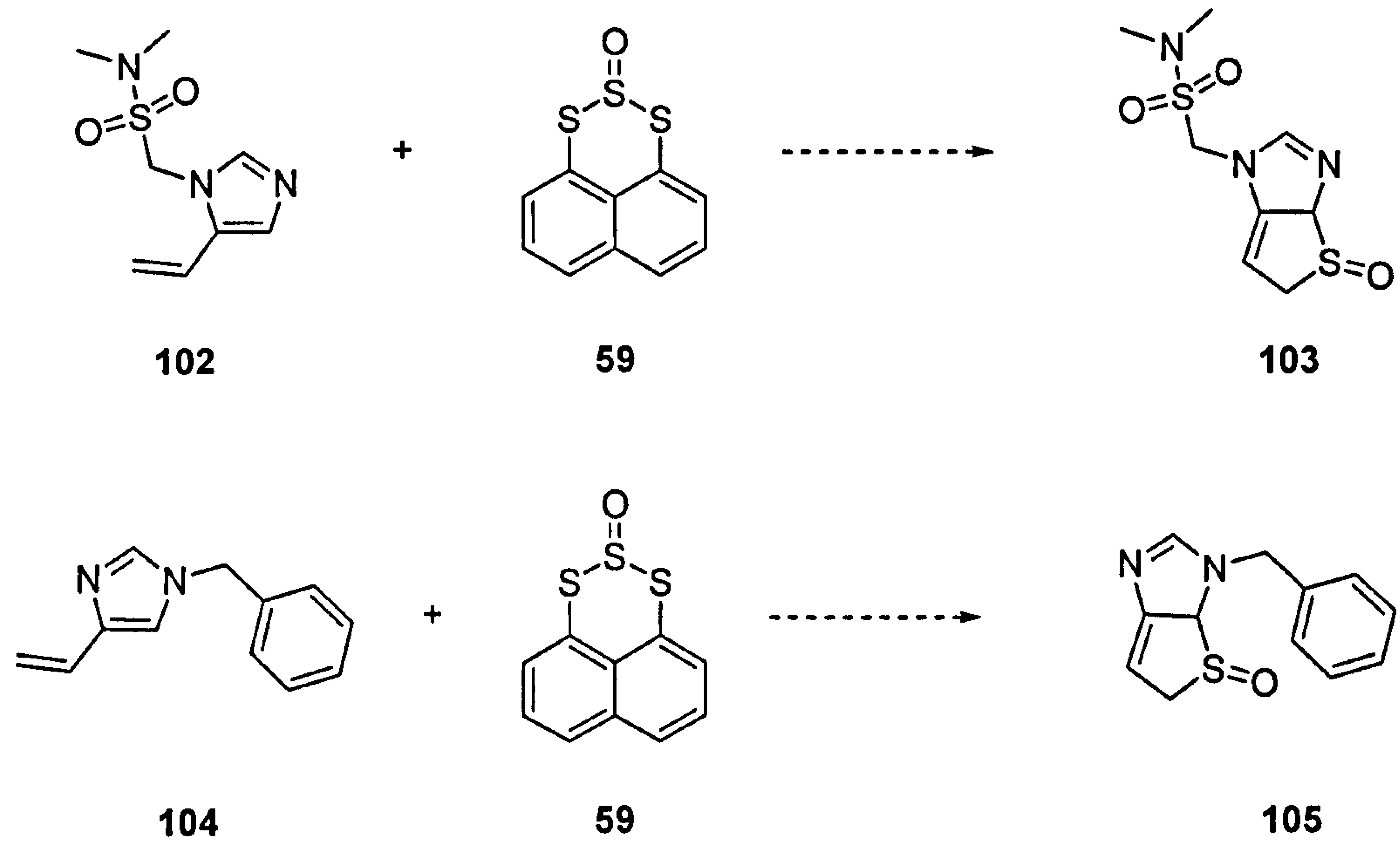
We then went on to explore the effect of different trisulfide oxide:diene ratios. In the case of myrcene it has already been mentioned that the ratio could be brought down to 1:2.5 without loss of yield (compare entries 13 and 17, Table 2.2). On the other hand with 2,3-dimethyl-1,3-butadiene and isoprene, we observed a sharp decrease in the yields when working with 1:2.5 ratios (entries 4 and 9, respectively).

Few experiment employing an even lower trisulfide oxide:diene ratio were carried out on myrcene and 2,3-diphenyl-1,3-butadiene. Working with 1:2 (entries 11 and 16, Table 2.2) and 1:1 ratios (entries 12, 19 and 21, Table 2.2) lowered the yields of the target 1,4-dihydrothiophene S-oxides.

Surprisingly, reacting a robust diene such as myrcene in the presence of an excess of trisulfide oxide **59** neither shortened the reaction time nor improved the yield (entry 20). One possible explanation of the latter result is that at these temperatures the stability of some of the 1,3-dienes is lower than that of the cyclic products.

Trapping experiments were also tried on cyclic dienes, such as 1,3-cyclopentadiene, 1,3-cyclohexadiene and 1,3-cyclooctadiene, without success (entries 22-29). Only the adduct of 1,3 cyclooctadiene has been previously reported.[16]

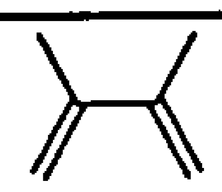
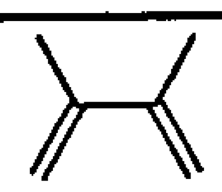
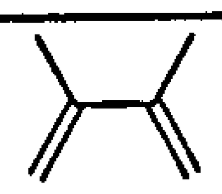
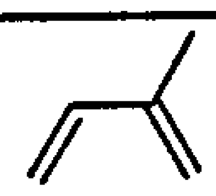
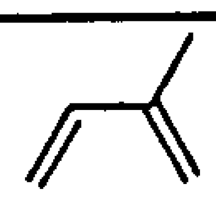
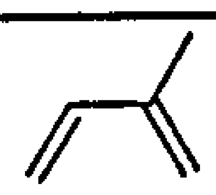
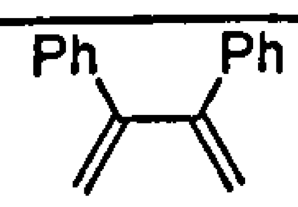
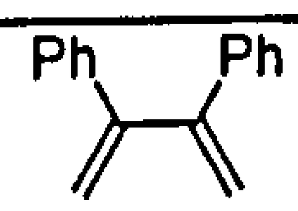
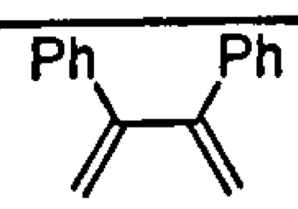
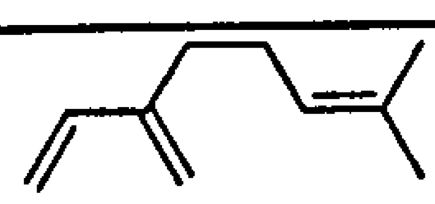
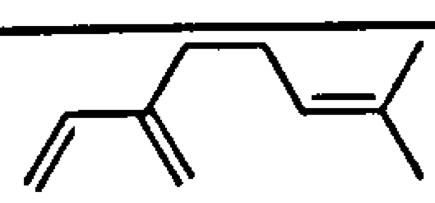
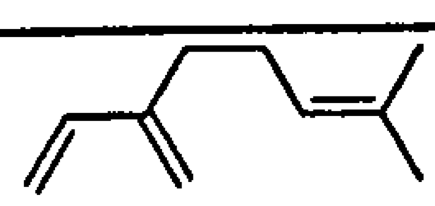
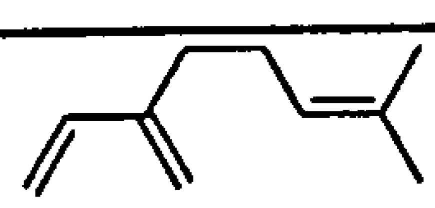
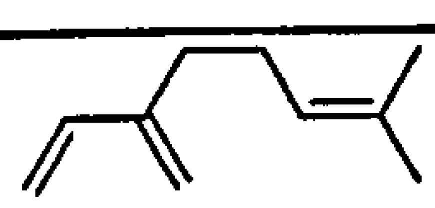
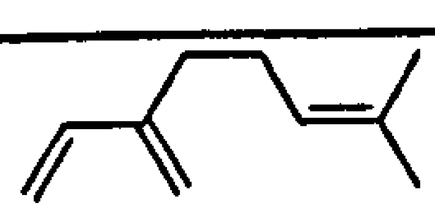
Also, we were kindly gifted by Prof. C. J. Lovely samples of structurally interesting imidazole derivatives 1-(N,N-dimethylsulfamoyl)-2-vinylimidazole **102** and 1-benzyl-4-vinylimidazole **104**, in order to try our chemistry on them (Scheme 2.41).

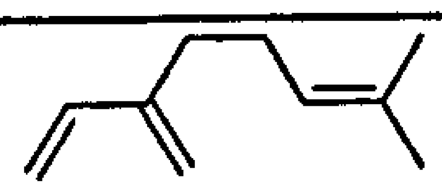
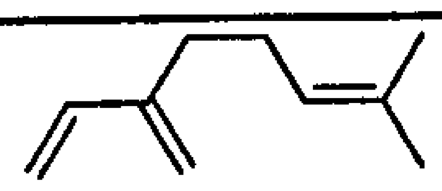
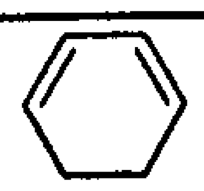
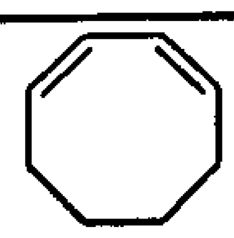
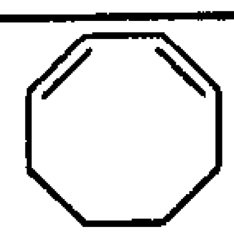
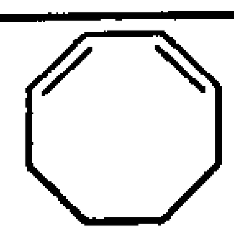
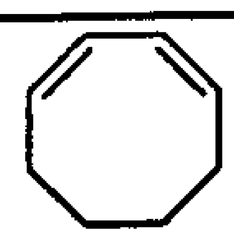
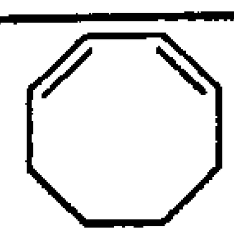


Scheme 2.41

Unfortunately, heating at reflux **102** or **104** in the presence of **59** did not result in the formation of **103** or **105**. Instead only around 50% of disulfide **59** was recovered along with complete recovery of **102** and **104**.

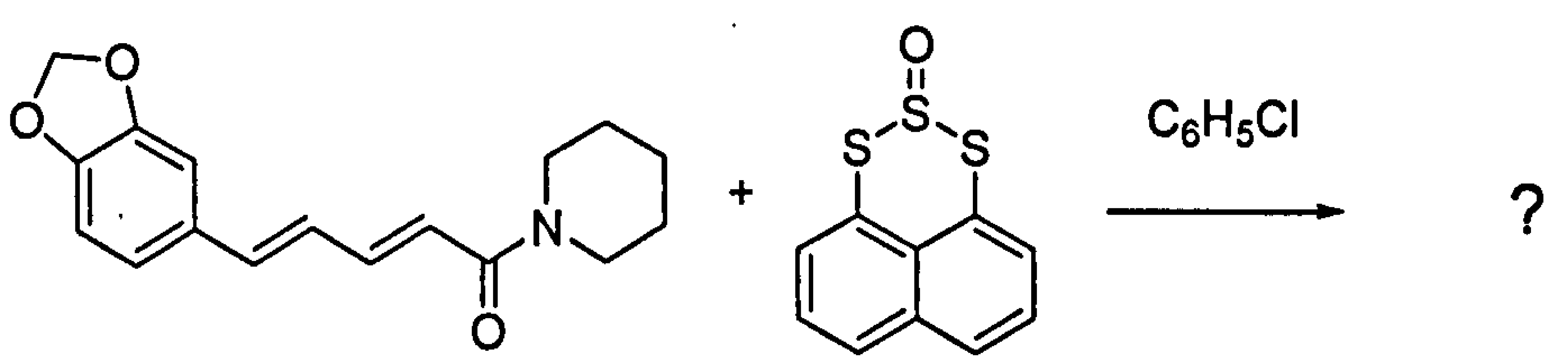
Table 2.2: Thermal decomposition of **59** in the presence of 1,3 dienes.

Entry	Diene	59: Diene Ratio	Solvent	Time (h)	Temp. (°C)	Thiophene (%)	Disulfide (%)[a]
1		1:3	$CDCl_3$	15	61	-	10
2		1:20	C_6H_5Cl	24	130	85	95
3		1:20	C_6H_5Cl	15	130	99	100
4		1:2.5	C_6H_5Cl	4.5	130	40	98
5		1:5	CH_3CH_2CN	35	98	< 1%	35
6		1:10	C_6H_5Cl	6	130	74	100
7		1:10	C_6H_5Cl	15	130	50	95
8		1:10	$C_6H_5CH_3$	26	110	65	100
9		1:2.5	C_6H_5Cl	4.5	130	41	90
10		1:2.5	C_6H_5Cl	6.5	130	65	100
11		1:2	C_6H_5Cl	3	130	51	100
12		1:1	C_6H_5Cl	3	130	41	95
13		1:10	C_6H_5Cl	1	130	65	70
14		1:10	$C_6H_5CH_3$	3	80	-	-
15		1:10	$C_6H_5CH_3$	24	110	71	100
16		1:2	C_6H_5Cl	3.5	130	87	100
17		1:2.5	C_6H_5Cl	4.5	130	87	98
18		1:2.5	C_6H_5Cl	6	130	93	100

19		1:1	C_6H_5Cl	6	130	36	100
20		2.5:1	C_6H_5Cl	4.5	130	84	98
21		1.1:1	C_6H_5Cl	5.5	130	38	98
22		1:25	$C_6H_5CH_3$	15	110	-	50
23		1:10	C_6H_5Cl	3	130	-	100
24		1:10	C_6H_5Cl	2	130	-	100
25		1:2	C_6H_5Cl	15	130	-	89
26		1:2	C_6H_5Cl	8	110	-	-
27		1:2.5	C_6H_5Cl	15	50	-	-
28		1:2.5	C_6H_5Cl	5	65	-	-
29		1:2.5	C_6H_5Cl	15	100	-	-

[a] Based on trisulfide oxide **55**.

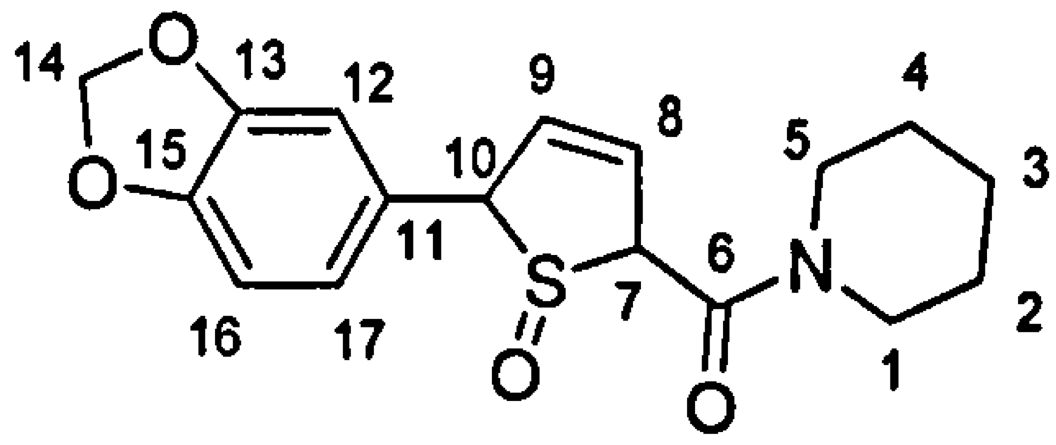
Another commercially available 1,3-diene is piperine **106**, which is extracted from black pepper (*Piper Nigrum*). Adopting the conditions we elected as most efficient (excess of diene, refluxing chlorobenzene) we carried out the experiment in Scheme 2.42.



106 **59** **107**

Scheme 2.42

The reaction was followed by TLC and after 16 hours the reaction was stopped. Work-up and column chromatography furnished two products. The first (a yellow oil, 30%) was characterized by [1]H, [13]C NMR and mass spectroscopy. The complexity of the spectra suggested the formation of more than one stereoisomer. We initially believed it to be the "expected" 1,4-dihydrothiophene S-oxides **107** (Figure 2.4).

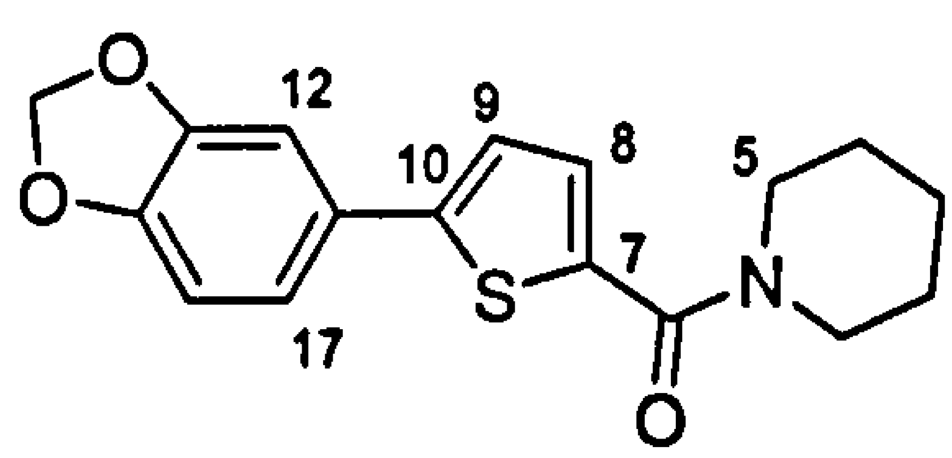


107

Figure 2.4

Following this assumption, protons 7-H/10-H and 8-H/9-H were annotated by NOESY and COSY. A through-space interaction between 5-H and both 7-H and 8-H was clearly visible. Although possessing a rather complicated pattern, NOESY showed no interaction between either 12-H and 8-H nor 7-H and 9-H; selected COSY relationships are 9-H to 10-H but not 7-H to 9-H. This assignment is uncertain, although it still remains our strongest one. The major inconsistencies are 7-H and 10-H as well as 7-C and 10-C, unexpectedly downfield for the proposed molecule. Also the mass value found with High-Resolution Mass Spectroscopy showes too a high discrepancy with the calculated value.

The second product (white crystals, 23%) had a molecular weigh of 315 and we hypothesized it could be thiophene **108** (Figure 2.5).



108

Figure 2.5

NOESY analysis confirmed through-space interactions between 5-H/8-H and between 9-H/17-H.

The structure was confirmed by X-ray analysis (Figure 2.6), for which crystals were obtained by the slow evaporation of a $CDCl_3$ solution of **108** in a NMR tube.

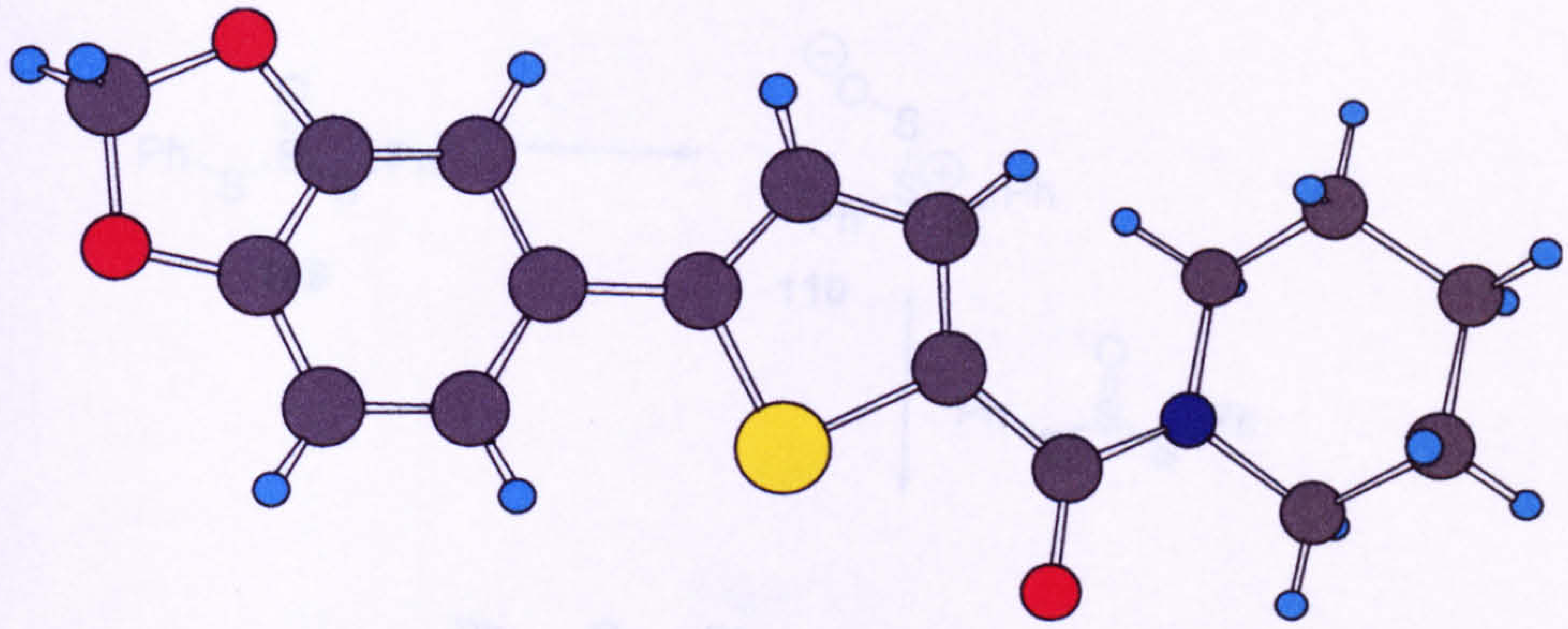


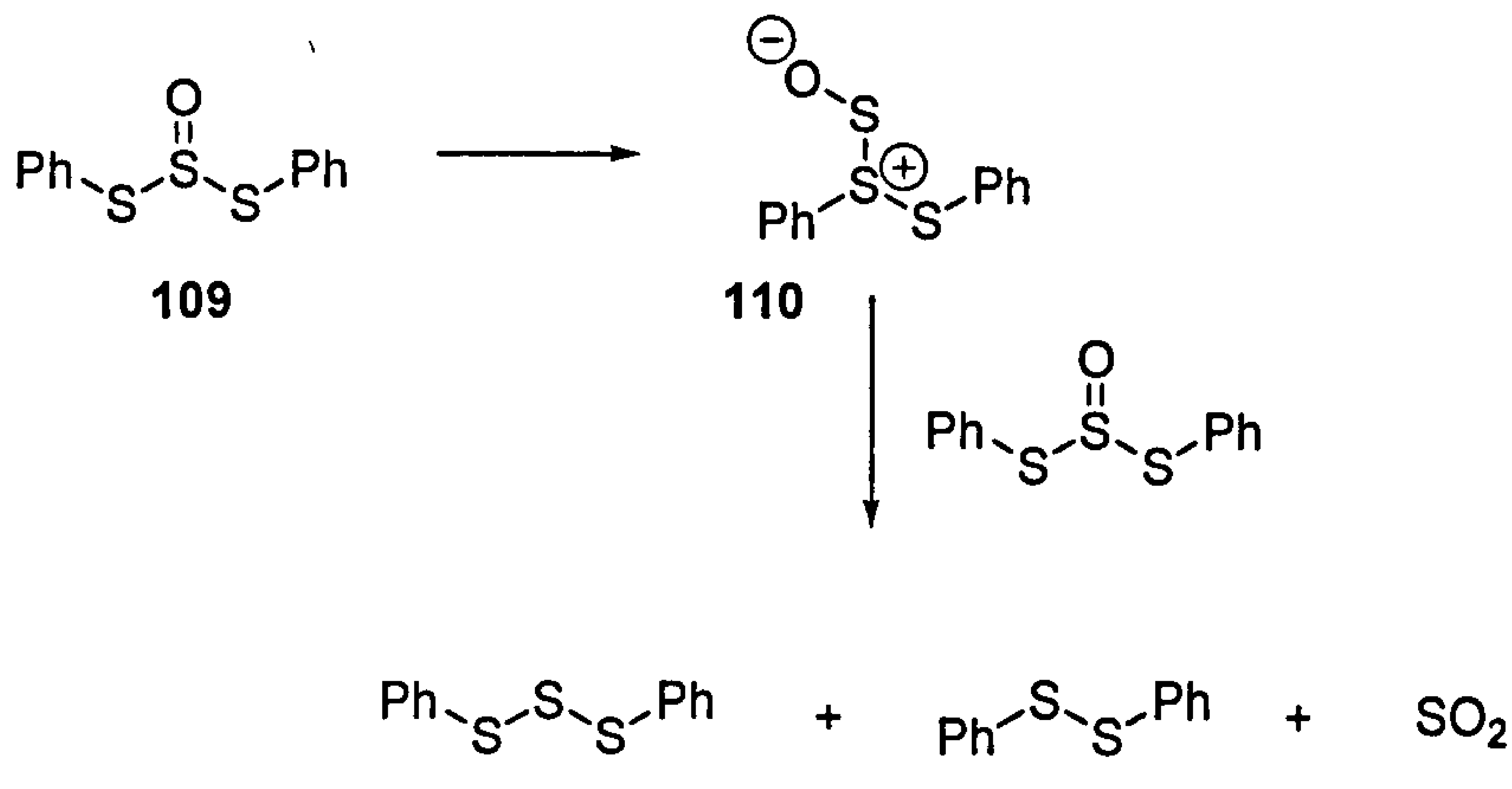
Figure 2.6

We hypothesised that if our assignement of compond **107** was correct, compound **108** could have been formed *via* a spontaneous dehydration of the 1,4-dihydrothiophene S-oxides (possibly triggered thermally). To check the correctness of this assumption we heated at reflux a pure sample of **107** in chlorobenzene but we did not observe formation of the thiophene derivative. Aromatization was also attempted by adding trifluoroacetic anhydride (TFAA) to a solution of **107** in dichloromethane, which is a known method to induce Pummerer reactions (*vide infra*). Yet again, no reaction took place. These results cast further doubts whether our assignment of compound **107** is correct.

The reaction in Scheme 2.42 was also attempted working with an excess of **59**. Lower yields (traces of products **107** and **108**), as before, demonstrated the inefficiency of this stoichiometry.

All these experiments confirmed **59** as a molecule capable of delivering SO by thermal decomposition both efficiently and with large applicability. We hypothesized that its chemical behaviour would be governed by the strain in the 1-8 *peri* interaction. As such, unstrained trisulfide oxides should not react analogously towards 2,3-dienes.

The thermal decomposition of *acyclic* trisulfide-2-oxides has been investigated in detail by Field and Lacefield. In contrast to **59**, thermolysis of acyclic trisulfide-2-oxides **109** gives rise to a mixture of trisulfide **111**, disulfide **112**, and sulfur dioxide (Scheme 2.43).[41,57]

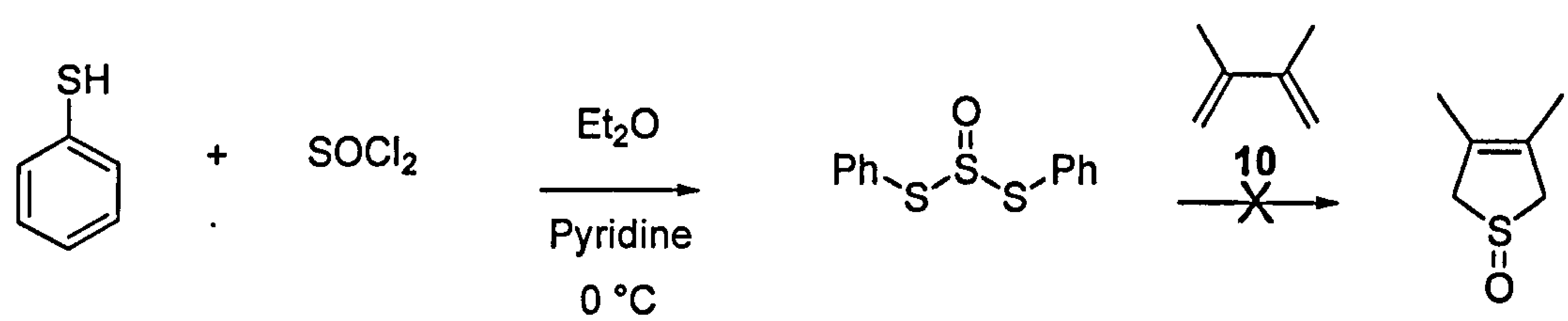


109 110 111 112 6

Scheme 2.43

Interestingly, the proposed mechanism postulates an initial rearrangement to a disulfide-sulfur monoxide adduct **110**, which rapidly reacts with a second molecule of trisulfide oxide **109**. To determine whether sulfur monoxide transfer is common to all trisulfide-2-oxides, we carried out the thermal decomposition of the phenyl derivative **109** in the presence of 2,3-dimethyl butadiene but did not observe the formation of any sulfoxide.

The synthesis of **109** was carried out in a fashion very similar to that of **59** and the yield was quantitative (Scheme 2.44).

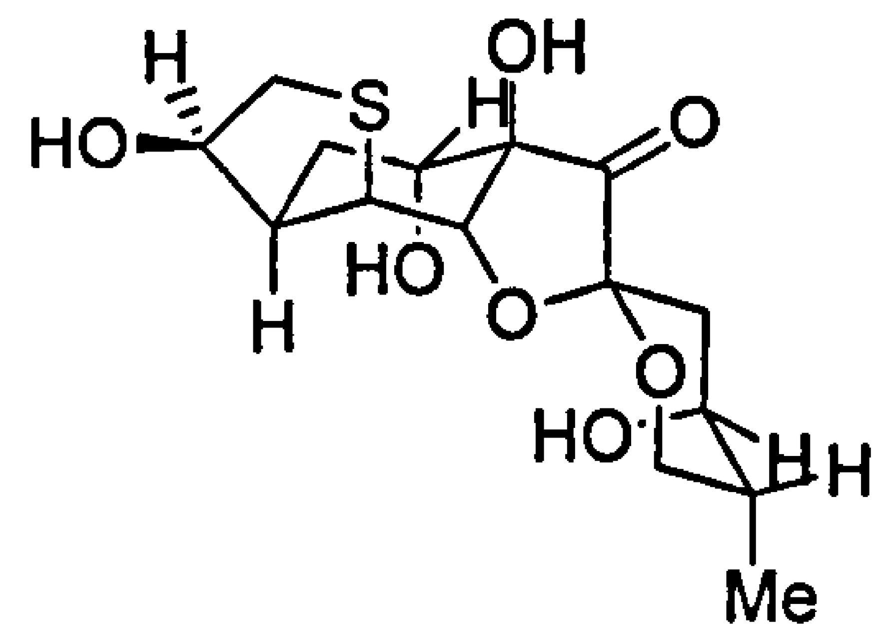


113 76 109 13

Scheme 2.44

2.3.5. Synthetic Applications of SO Transfer.

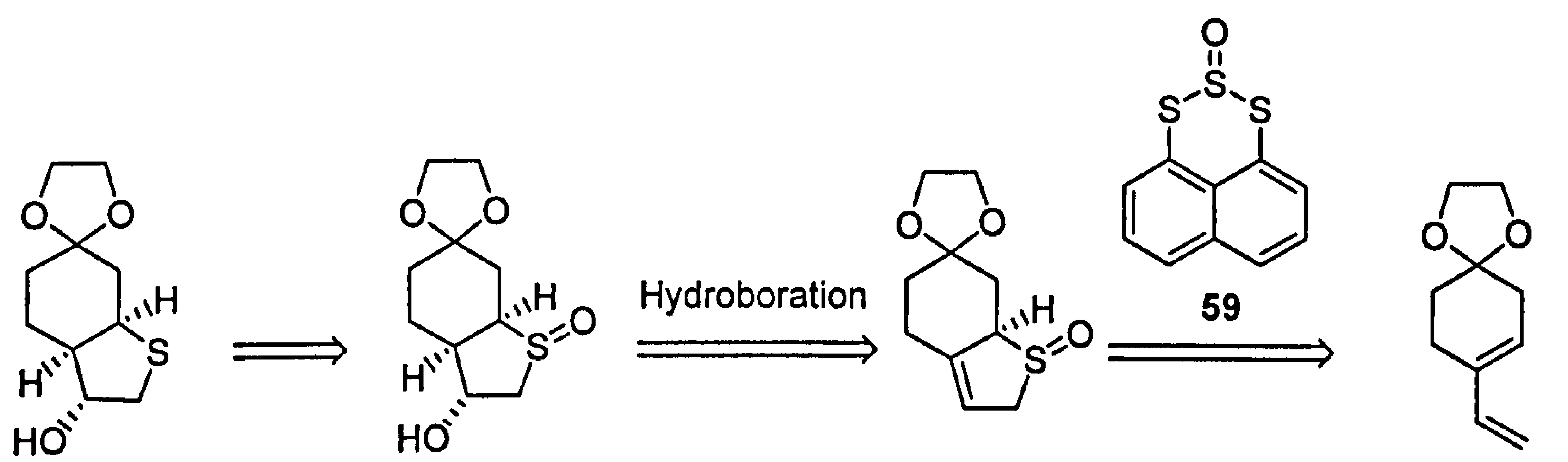
The possibility of transforming dienes to dihydrothiophenes oxides in one step prompted us to seek synthetic applications of this new methodology. We focused on a novel approach towards the synthesis of (+)-breynolide **114**, the aglycon hydrolysis product of the antibiotic disaccharides Breyins A and B (Figure 2.7).[58]



114

Figure 2.7

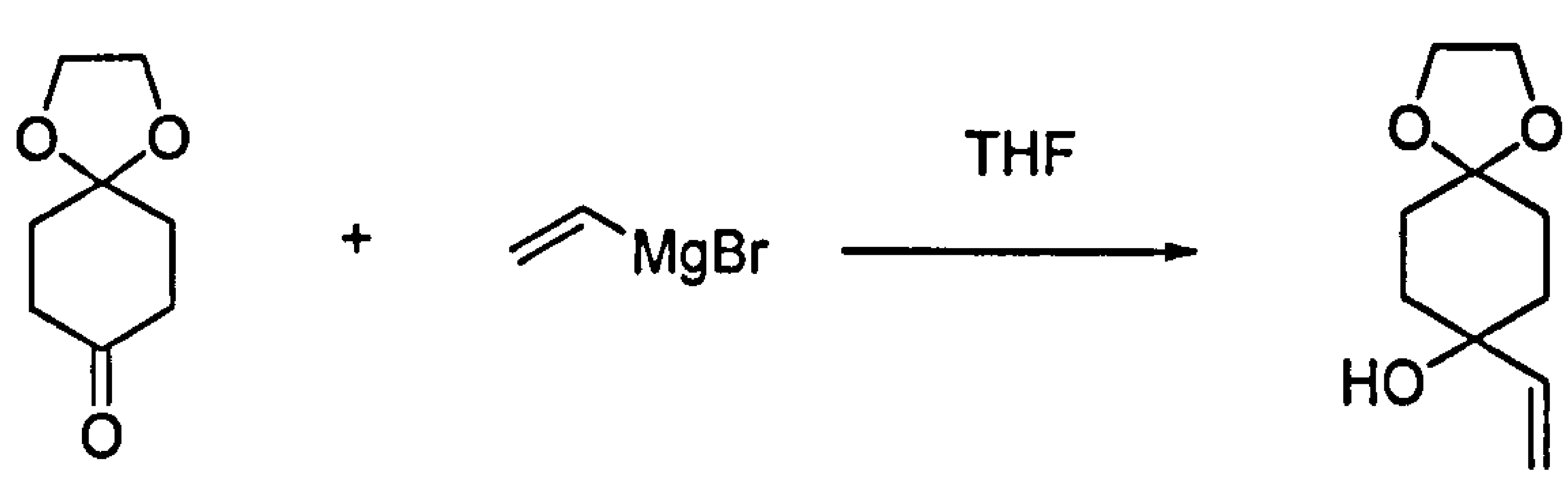
One of the interesting features of the molecule is the *cis* geometry of the tetrahydrothiophene-cyclohexane fused rings. As a model study, we envisaged that SO trapping of diene **118** would provide an ideal platform for a stereo- and regioselective hydroboration of the double bond, followed by reduction of sulfoxide **116** to sulfide **115** (Scheme 2.45). The acetal protected ketone is ideally positioned for further transformations.



115 116 117 118

Scheme 2.45

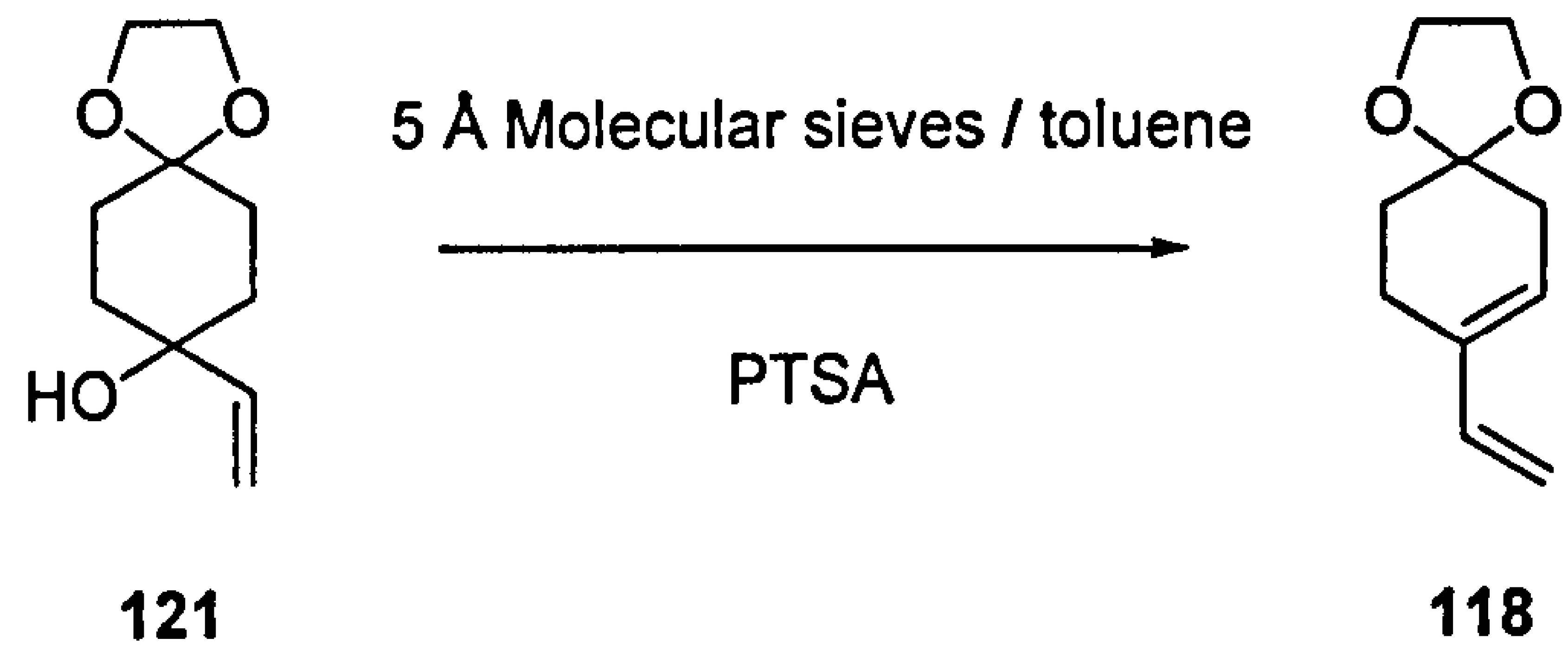
The preparation of **118** has been previously reported.[59] Treatment of commercially available 1,4-cyclohexanedione *mono*-ethylene ketal **119** with vinylmagnesium bromide afforded **121** in 90% yield (Scheme 2.46).



119 120 121

Scheme 2.46

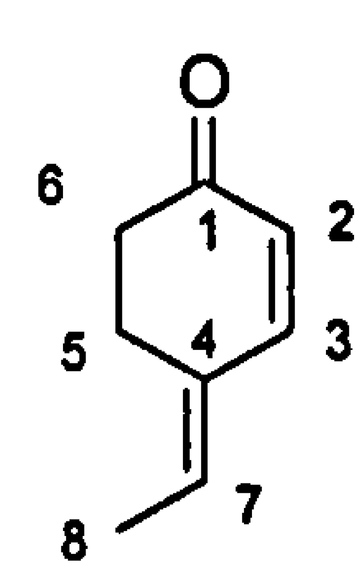
Acid-catalysed alcohol dehydration with molecular sieves gave capricious results (Scheme 2.47). Yields were never satisfactory although similar to those reported in the literature (36%).



Scheme 2.47

Nevertheless, with diene **118** in hands, we attempted the formation of 2,4-dihydrothiophene **117** by reacting **118** with **59** (1:1) in refluxing chlorobenzene. Disulfide **61** was recovered quantitatively, yet TLC analysis showed a large number of compounds to be present. Separation by column chromatography did not help to determine the nature of most of them. Based on our previous observations we attempted the reaction a second time, using an excess of diene (2.5:1). Again decomposition products made the separation very complicated. Fractions from column chromatography were not acceptably pure yet ^{1}H NMR gave strong indication that the target compound **117** had formed, although in traces.

Our attention was drawn however by the presence of another set of signals dominating the spectrum. Repetition of the reaction on a much bigger scale allowed us to separate some chromatographic fractions where only this compound was present. Spectroscopic analysis suggested dienone **122** as the major product (Figure 2.8).



122

Figure 2.8

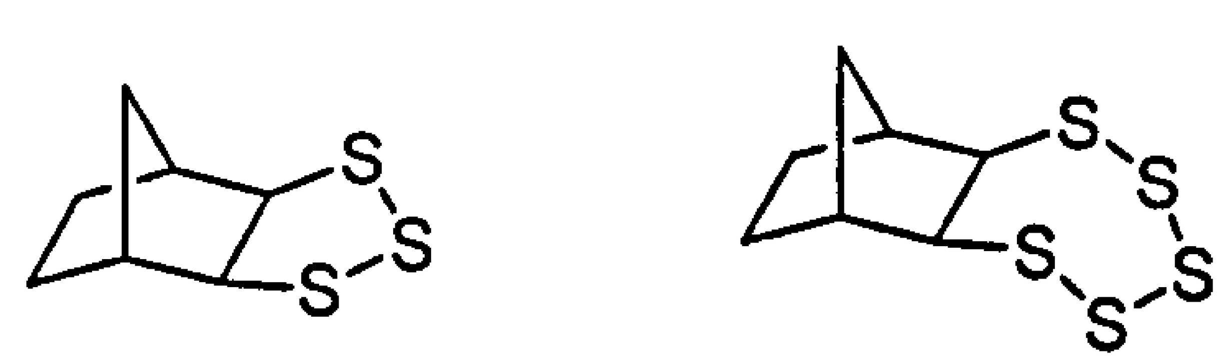
Disappearance of the signals around 4 ppm (^{1}H NMR) and appearance of a signal at 199.5 ppm (^{13}C NMR) were indicative of the loss of the ketal protection. Furthermore the presence of one doublet at 2 ppm ca. (CH_3), only two CH_2 signals (^{13}C NMR) and a molecular mass of 122 finally confirmed the structure as **122**. Elucidation of the stereochemistry about the double bond was assisted by NOESY. Of the two doublets belonging to 2-H and 3-H (5.8 ppm and 7 ppm), one would already expect the latter to be more downfield. Indeed the signal at ~ 5.8 ppm showed no through-space interaction with other protons but with that at 7 ppm. The signal at 7 ppm, on the other hand, gave rise to interaction with the multiplet at 6 ppm (7-H). These observations assigned unequivocally 2-H, 3-H and the *trans* geometry about the double bond. That was confirmed by NOESY signals between the CH_3 doublet and the 5-H multiplet, which in turn also distinguished between the two CH_2 signals.

2.3.6. Trapping of Transient Sulfur Species.

The instability of free SO has already been mentioned. In the literature it is reported to rapidly decompose to S_3 which then equilibrates to the more stable allotropic form S_8 (see Scheme 2.37). The chemistry of S_3 has been studied and has interesting theoretical facets.[44]

We first wanted to test whether the decomposition of the trisulfide oxide was independent of the presence of 1,3 dienes. A solution of **59** in chlorobenzene was refluxed overnight. The detected product was disulfide **61** (90%); starting material accounted for the remaining 10%. Refluxing a solution of the same concentration in the presence of myrcene (2.5 eq.) reached the same ratio of **61** to **59** of 9:1 after 2.5 hours. It seemed that decomposition of pure trisulfide oxide was accelerated by the presence of a diene.

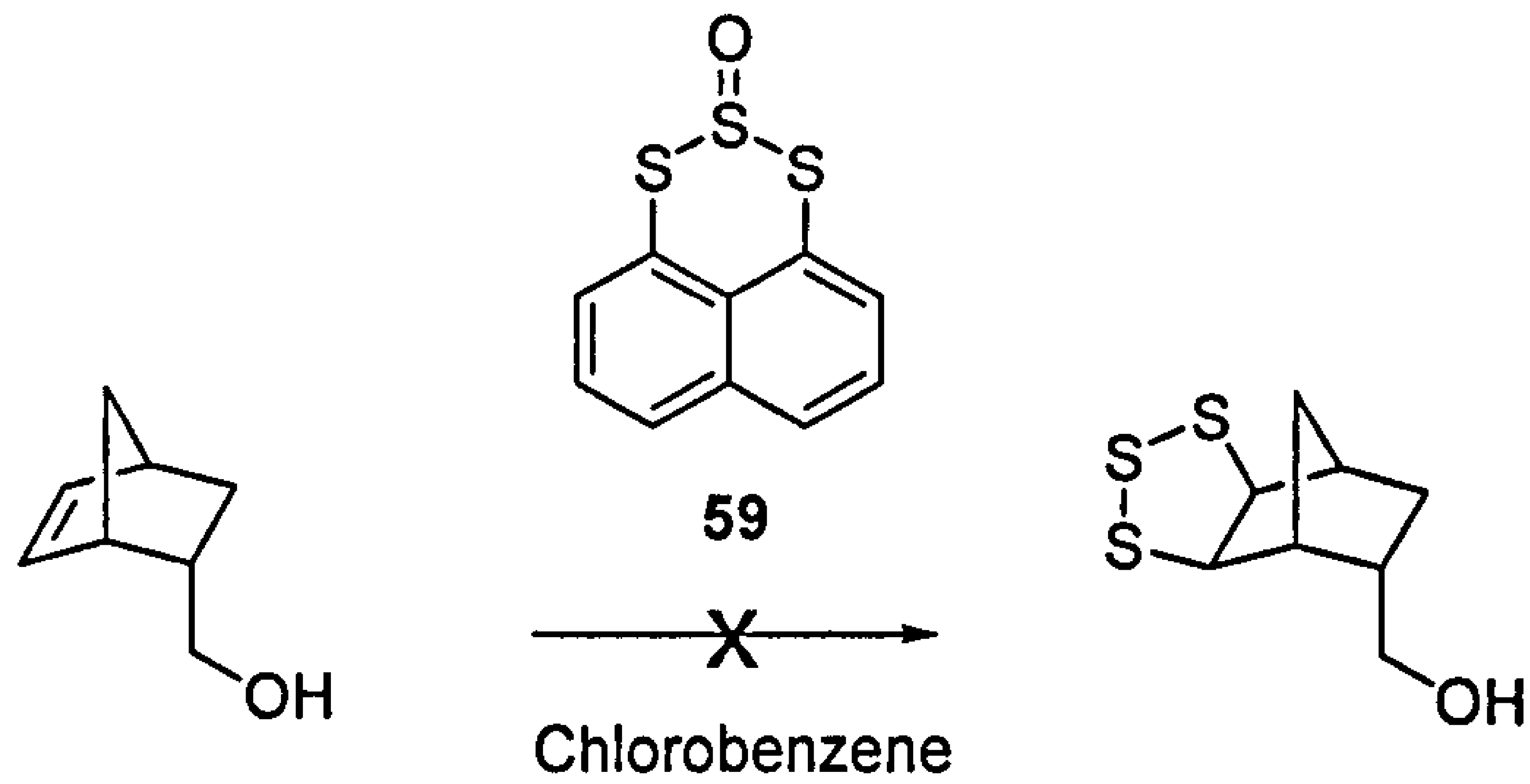
Norbornene is known to react with sulfur allotropes to form norbornanetrithiolane **123** and norbornanepentathiepane **124** (Figure 2.9).[60]



123 **124**

Figure 2.9

We envisaged that performing trisulfide oxide decomposition in the presence of a norbornene derivative could trap a transient S_3 species. We had previously synthesized **125** (see Chapter 1, Paragraph 1.4 - Experimental Section), which we hoped would yield a product analogous to **123**.



Scheme 2.48

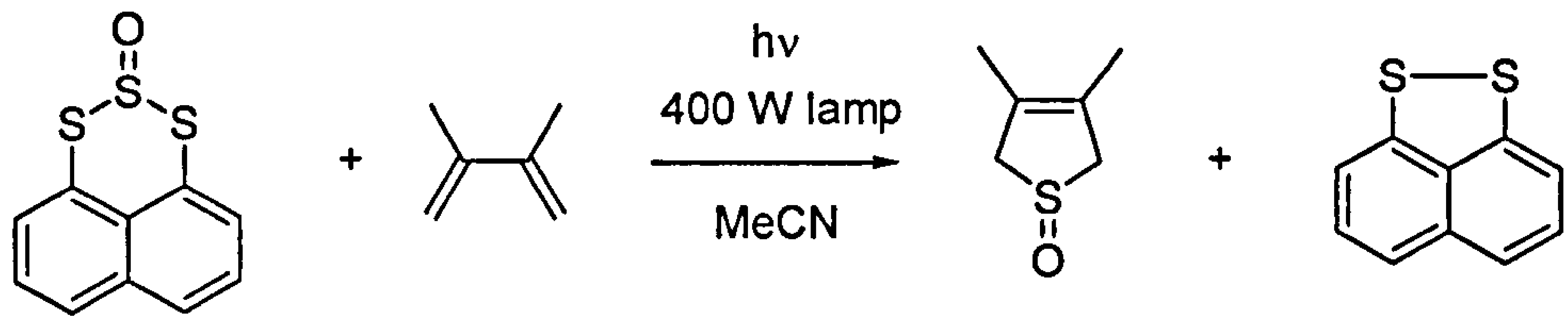
A mixture of **125** and **59** was refluxed in chlorobenzene for 6h. TLC showed no new product (Scheme 2.48). The mixture was then stirred at room temperature overnight. ^{1}H NMR on the crude sample revealed the presence of **125** and disulfide **61** and little **59** left; formation of **126** could have been expected as elemental sulfur is known to add to norbornene but the reaction is reported to proceed exclusively in DMSO or DMS.[61]

2.3.7. Photochemical Trapping Experiments with 1,3-Dienes.

As reported in the introduction, loss of SO from ethylene episulfoxide can be also achieved photochemically. Also, work by Furukawa on similar systems (e.g Scheme 2.18) suggested that trisulfide oxide **59** could be a good candidate for SO transfer under photochemical conditions. He reported successful reactions using a large array of solvents (CH_2Cl_2, THF, ethanol, acetonitrile).

We first tested the possible decomposition of **59** when irradiated with a 400 W medium-pressure Hg lamp (> 254 nm). The solvent of choice was chlorobenzene. Use of this high boiling solvent avoided rapid evaporation. Although disappearance of **59** was observed, no characterizable product could be separated.

We then adopted one of the solvents utilized by Furukawa. Indeed, a 1:1 mixture of **59** and **10** in acetonitrile irradiated for 1 hour gave rise to the formation of disulfide **61** and the target molecule **13**, although the latter only in traces (^{1}H NMR) (Scheme 2.49). In this case an evident destructive decomposition process was taking place. The solution was brown in colour and a black solid could be seen floating in solution.



59 10 13 61

Scheme 2.49

Switching solvents to chlorobenzene and using an excess of **10** resulted in a marked improvement in terms of yield. After 2 hours of reaction **59** was transformed almost quantitatively into **61** and 40% of **13** was formed.

In order to determine whether the improvement was due to the excess of diene or the specific solvent, we repeated the reaction in acetonitrile using 20 equivalents of 2,3-dimethyl-1,3-butadiene. After column chromatography only traces of **13** were detected thus underlying the importance of the solvent.

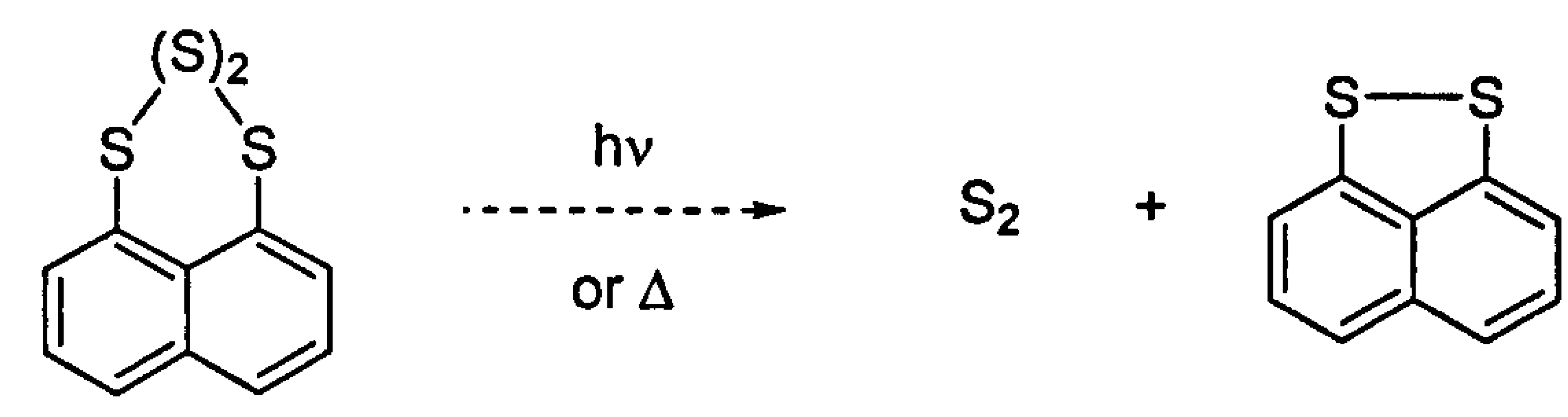
Normal daylight was also able to trigger the reaction. A 1:3 mixture of **59** and **10** in $CDCl_3$ was exposed to light irradiation from a normal table lamp for 1 hour. Along with quantitative recovery of **61**, 40% of **13** was produced.

As for the thermal decomposition in non-degassed solvents, traces of thiosulfinate **100** were always found in the reaction mixtures. To establish whether this compound originated from the reaction pathway or by oxidation of the disulfide, we irradiated a pure sample of **61** in non-degassed chlorobenzene. Indeed **100** was formed again in traces, along with some decomposition to a tarry black solid.We concluded that photochemical activation of trisulfide oxide **59** was possible but the results were inferior compared to those under thermal conditions.

2.3.8. Synthesis of a Novel S_2 Transfer Molecule.

Diatomic sulfur also plays a rather interesting role in chemistry, both from a mechanistic and synthetic point of view.[62] Curiously, this molecule has been detected by the Hubble telescope in Jupiter's dark spot resulting from the impact of the G fragment of the Comet Shoemaker-Levy 9.[63]

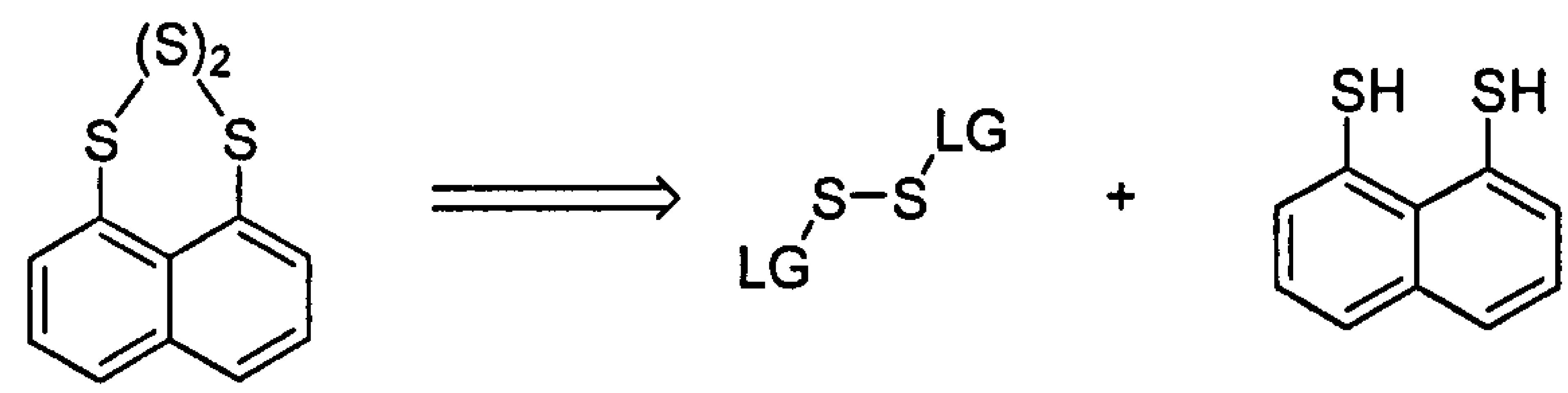
We envisaged that molecule **127**, for the same argument invoked for **59**, would have been a suitable precursor for the *in situ* formation of S_2 (Scheme 2.50).



127 61

Scheme 2.50

Synthesis of **127** was attempted according to the retrosynthetic analysis in Scheme 2.51



127 128 82

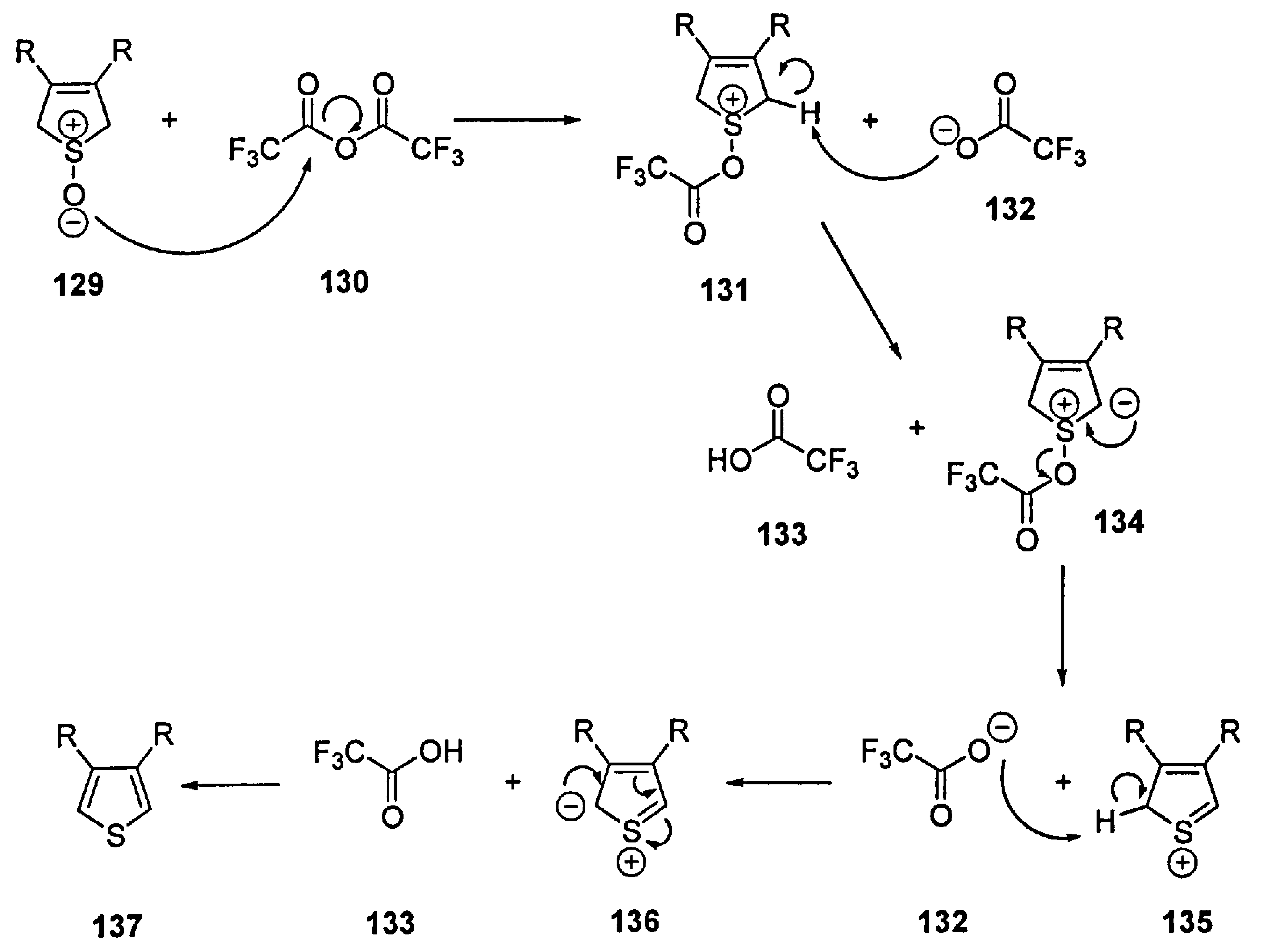
Scheme 2.51

We had already determined that reduction of **61** to **82** could be achieved with both LAH or $NaBH_4$. We therefore turned or attention to commercially available compounds analogous to **128** bearing good leaving groups. The only reagent we employed was sulfur monochloride S_2Cl_2. A one-pot LAH reduction of **61** followed by addition of S_2Cl_2 afforded complete recovery of **61**.

Although work-up and isolation of dithiol **82** prior to the addition of S_2Cl_2 could have led to better results, time constraint impeded us to carrying on with the exploration of this chemistry. However we feel it would be worth the effort trying to prepare **127** and test its thermal and photochemical behaviour.

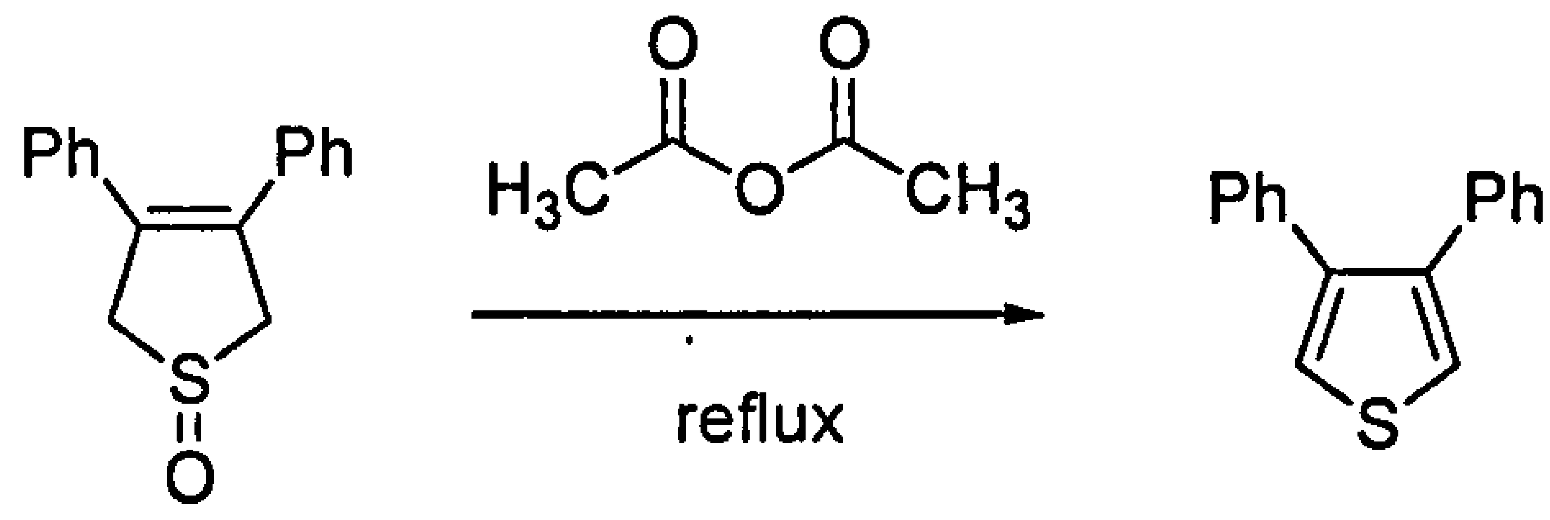
2.3.9. Pummerer Transformation of 1,4-Dihydrothiophene S-Oxides.

As mentioned at the beginning of the chapter, 1,4-dihydrothiophene S-oxides **2** are synthetically interesting because they can potentially undergo the Pummerer reaction to form the useful thiophene functionality. The use of anhydrides to initiate the Pummerer reaction is well known.[64] A potential mechanism for the reaction of sulfoxide **129** with TFAA is shown below (Scheme 2.52).



Scheme 2.52

Under typical Pummerer conditions, **132** would attack the carbon of the C-S double bond and form a 2-acyl-1,4-dihydrothiophene adduct. On the contrary, to maximise the chance of promoting the reaction as depicted in Scheme 2.52, sulfoxides with R groups capable of stabilizing intermediate **136** were needed. We therefore assumed that among the compounds we synthesized *via* SO trapping, 2,3-diphenyl-1,4dihydrothiophene S-oxide was the best candidate to succeed. Heating a solution of **14** in neat acetic anhydride at 110 °C for 15 hours gave no reaction. However, by heating at reflux the mixture for 3 hours a new compound was revealed by TLC. Purification by column chromatography yielded a white crystalline solid (63%). ^{1}H NMR showed disappearance of the aliphatic hydrogens (4-4.5 ppm) and formation of new peaks in the aromatic area, although overlapping with phenyl protons and thus impossible to annotate. However ^{13}C-NMR spectroscopy and mass spectroscopy confirmed the assignment as **138** (Scheme 2.53).

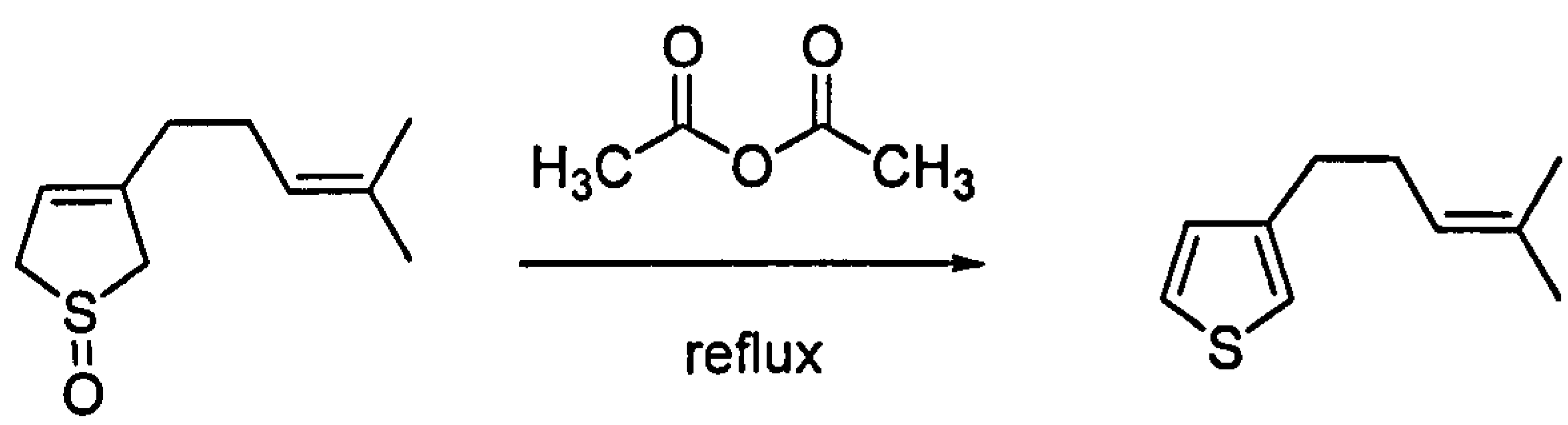


14 138

Scheme 2.53

The same reaction was carried out on 2,3-dimethyl-1,4-dihydrothiophene S-oxide **13**. However after 1.5 hours the solution turned black. TLC analysis showed that no product had been formed. ^{1}H NMR spectroscopy on the crude material showed disappearance of the α-sulfoxide aliphatic hydrogen signals but a definitive assignment could not be achieved. Mass spectroscopy was also not conclusive.

3-(4-Methyl-penta-3-ene)-1,4-dihydroxythiophene S-oxide **46** was subjected to two different Pummerer conditions.[65] In the first case it was refluxed in neat acetic anhydride for 2 hours to furnish after column chromatography a light yellow oil (50%). Spectroscopic analysis confirmed the success of the reaction and formation of thioperillene **139**[66], a constituent of hop and rose oil (Scheme 2.54).



46 139

Scheme 2.54

The addition of a "hotter" anhydride such as TFAA was performed at room temperature to a solution of **46** in dichloromethane. After 2 hours of reaction, **139** was obtained pure in 39% yield. The reaction was repeated performing the anhydride addition at zero degrees and triethylamine was added to the mixture to neutralize the trifluoroacetic acid being formed. Using these conditions the reaction was unsuccessful. The use of tosic acid was attempted on 2-methyl-1,4-dihydroxythiophene S-oxide **32**. The mechanism of reaction is very similar to that depicted in Scheme 2.53. One difference is that the side product of this reaction is water, as opposed to acids when using anhydrides. The reaction is typically carried out in refluxing toluene, using a Dean-Stark apparatus. After 2 hours the reaction solution went black and no product could be characterized.

2.3.10. Conclusions and Future Work.

1. Trisulfide oxide **59** is a powerful tool for the transformation of simple acyclic 1,3-dienes into 1,4-dihydroxythiophene S-oxides. This transformation can be achieved thermally in a series of solvents; the best yields, however, were observed using dichlorobenzene at 132 °C. Under such conditions exceptionally good results are obtained. In fact, confirming our hopes, trisulfide oxide **59** showed consistently better performance than Harpp's episulfoxide, with higher yields and shorter reaction times.

2. The same transformation can also be triggered photochemically. Our study was only explorative due to time constraints; it would be thus very interesting to test the reaction under various photochemical conditions and on substrates that did not react under thermal conditions (such as cyclic 1,3-dienes).

3. Application of the same methodology to more complex systems gave some intriguing results. Piperine **106** furnished two adducts. The first is possibly **107** and the second is thiophene **108**. Diene **118** underwent a totally unexpected ketone acetal deprotection and isomerisation. Both these results opened up a series of questions on the mechanism of action of molecule **59**.

4. One of the really attractive features of this novel trisulfide oxide is that under almost every reaction condition the recovery of the parent disulfide **61** is virtually quantitative. The one-step re-conversion of **61** to **59** with cheap thionyl chloride makes this system a real example of a recyclable molecule.

5. We have demonstrated that the 1,4-dihydroxythiophene S-oxides so obtained can be transformed into aromatic thiophenes in the presence of different anhydrides. The infrequency of this variation of the Pummerer reaction furnishes *stimuli* for the quest of possible synthetic applications.

Nonetheless some questions are still open. For example whether the mechanism of the SO transfer goes via "free" SO or some radical or ionic intermediate. This could be elucidated by using the 2,4-hexadiene isomers (*tt*-**24**, *ct*-**25** and *cc*-**26**) as the trapping substrates. Unfortunately time constraint impeded the full exploration of the theoretical aspects and synthetic applicability of **59**.

Moreover, if our assumption that the driving force for the loss of SO lies in the strain relief holds true, we feel that the 1,8-disubstituted naphthalene could represent a useful framework for the construction of other molecules capable of transferring other diatomic units (e.g. SeO, S_2).

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected.

Infra-red spectra were recorded on a Perkin-Elmer Paragon 1000 Fourier transform I.R. spectrometer.

^{1}H NMR were recorded using a Bruker AM360 or AM400 spectrometer in deuterochloroform, unless otherwise stated, referenced to TMS (δ 0). Chemical shifts are in parts per million (δ ppm). Coupling constants are in Hertz (*J* Hz). The following abbreviations are used: bs-broad singlet, s-singlet, d-doublet, dd-double doublet, t-triplet, m-multiplet.

^{13}C NMR were recorded on a Bruker AM360 or AM400 spectrometer in deuterochloroform unless otherwise stated. Chemical shifts are in parts per million (δ ppm).

Mass spectra were recorded on a Jeol AX505W spectrometer (EI).

Flash chromatography was carried out according to Still's paper[67] using Merck silica gel 60 (4063 μm). *Analytical t.l.c.* was carried out on Merck (aluminium sheets) silica gel 60 F_{254} plates using short wave (254 nm) UV light, Ninhydrin spray (from BDH), $KMnO_4$ or anisaldehyde to visualise components.

Solvents and reagents were purified as follows:

Benzene- Distilled from calcium hydride and stored over 4 Å molecular sieves.

Dichloromethane - Distilled from calcium hydride and stored over 4Å molecular sieves.

DMSO – Purified by distillation from calcium hydride using a high pressure vacuumpump.

Pyridine – Refluxed over calcium hydride and distilled prior to use.

Tetrahydrofuran - Freshly distilled from sodium and benzophenone.

Toluene – Distilled from calcium hydride and stored over 4 Å molecular sieves.

All other reagents and solvents were used as received.

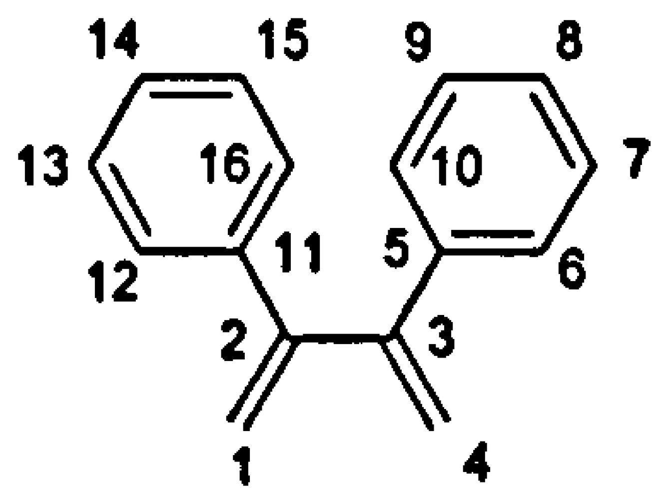
Cooling mixtures were obtained as follows:

0 °C: ice/water.

-5 °C to –78 °C: acetone/dry ice.

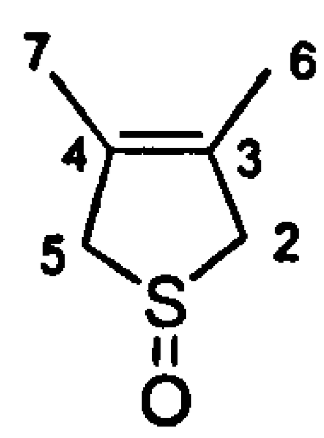
Unless otherwise stated, all reactions in non aqueous media were carried out under an atmosphere of argon in oven-dried glassware.

2,3-Diphenyl-1,3-butadiene (11).[56]



A 100 cm^3round bottom flask was charged with DMSO (13 cm^3) and NaH (60% in oil, 1g, 25.10 mmol). The mixture was heated at 75 °C for 30 minutes. The flask was then cooled down to 30 °C. The dark grey solution was added dropwise of a solution of diphenylacetylene **101** (2g, 11.20 mmol) in DMSO (20 cm^3). The flask was then heated at 95 °C for 2.5 hours. The resulting brown reaction mixture was cooled to room temperature and poured onto a mixture of water and ice (200 cm^3). The mixture was extracted with diethyl ether (5 x 50 cm^3). The combined organic layers were then washed with water and dried over $MgSO_4$. Purification by column chromatography was performed with 60-80 petrol ether to yield 2,3-diphenyl-1,3-butadiene **11** (680 mg, 26%) as a yellow oil; R_f 0.15 (60-80 petroleum ether); δ_H(360 MHz; $CDCl_3$) 5.09 (2H, s, 1-H_a and 4-H_a), 5.39 (2H, s, 1-H_b and 4-H_b), 7.10-7.25 (10H, m, 6-H to 10-H, and 12-H to 16-H); *m/z* (LREI) 206 (M^+; 17%), 193 (99), 178 (47), 115 (100), 104 (45), 91 (74).

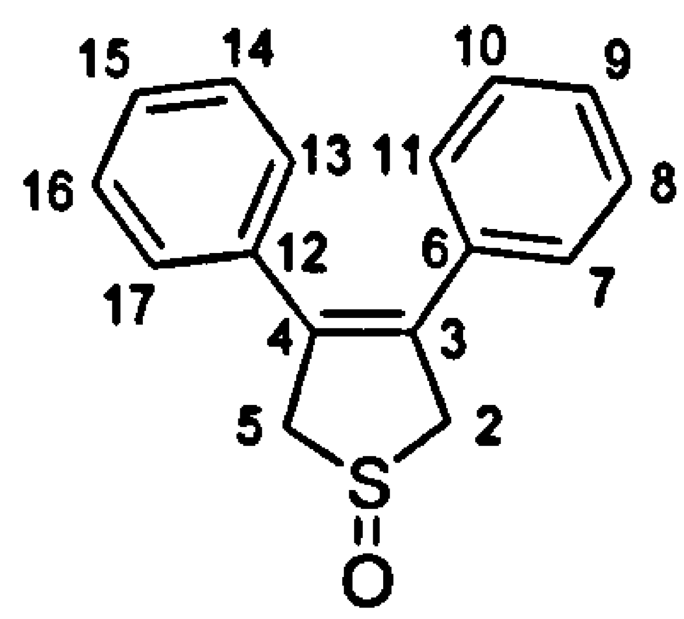
2,5-Dihydro-3,4-dimethylthiophene 1-oxide (13).[22]



A solution of 2,3-dimethyl-1,3-butadiene **10** (0.95 cm^3, 8.4 mmol) and 1,2,3-trithia-phenalene 2-oxide **59** (100 mg, 0.42 mmol) in degassed chlorobenzene (50 cm^3) were heated at reflux for 15 h, until **59** was fully consumed. The solvent was removed under reduced pressure. The oily residue was dissolved in methanol (50 cm^3) and the solvent removed again. Purification by column chromatography was performed with 60-80 petroleum ether first, to yield [1,8-*c,d*]-1,2-dithiole **61** (80 mg, 100%). The column was then flushed with ethanol to yield **13** (57 mg, 99%) as an yellowish oil; υ_{max} (nujol)/cm^{-1} 1050 (SO); δ_H(400 MHz; $CDCl_3$) 1.71 (6H, s, 6-H and 7-H), 3.38 (2H, d, *J* 16.6, 2-H_a and 5-H_a,), 3.76 (2H, d, *J*

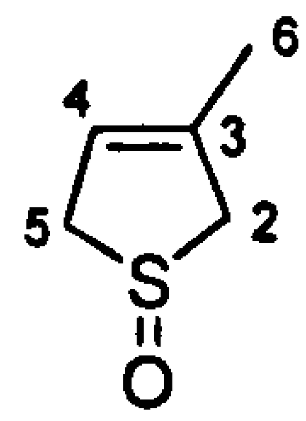
17.1, 2-H_b and 5-H_b,); δ_C (100 MHz; $CDCl_3$) 14.9 (q, 6-C and 7-C), 64.6 (t, 2-C and 5-C), 126.4 (s, 3-C and 4-C); *m/z* (LREI) 130 (M^+; 83%), 113 (7), 99 (6), 82 (38), 67 (100), 54 (21).

2,5-dihydro-3,4-diphenylthiophene 1-oxide (14).[22]



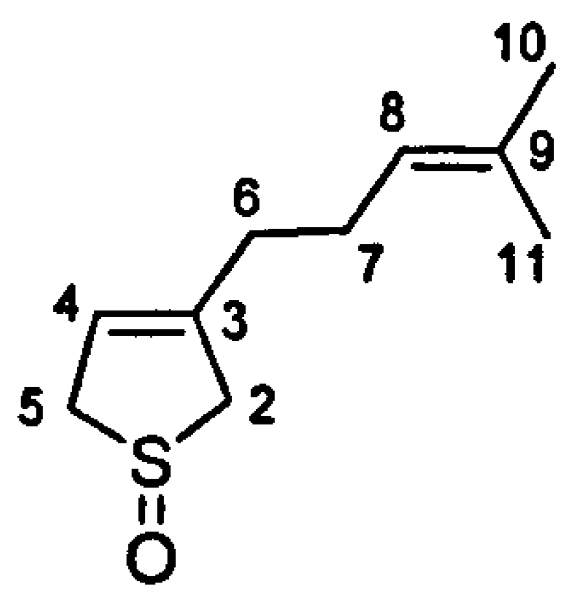
A solution of 2,3-diphenyl-1,3-butadiene **11** (0.721 mg, 3.15 mmol) and 1,2,3-trithiaphenalene 2-oxide **59** (300 mg, 1.26 mmol) in degassed chlorobenzene (50 cm^3) was heated at reflux for 6.5 h, until **59** was fully consumed. The solvent was removed under reduced pressure. The oily residue was dissolved in methanol (50 cm^3) and the solvent removed again. Purification by column chromatography was performed with 60-80 petroleum ether first, to yield [1,8-*c*,*d*]-1,2-dithiole **61** (240 mg, 100%). The column was then flushed with ethanol to yield **14** (208 mg, 65%) as a colourless oil; υ_{max} (nujol)/cm^{-1} 1038 (S=O); δ_H(360 MHz; $CDCl_3$) 4.05 (2H, d, *J* 16.2, 2-H_a and 5-H_a), 4.40 (2H, d, *J* 16.2, 2-H_b and 5-H_b,), 7.15-7.25 (10H, m, 7-11 and 13-17-H); δ_C (90 MHz; $CDCl_3$) 64.8 (s, 2-C and 5-C), 128.4-129.0 (d, 7-11 and 13-17-C), 132.4 (s, 3-C and 4-C or 6-C and 12-C), 135.9 (s, 3-C and 4-C or 6-C and 12-C); *m/z* (LREI) 254 (M^+; 6%), 236 (16), 205 (68), 190 (100), 178 (14), 86 (59); *m/z* (HREI) calcd for $C_{16}H_{14}SO$ 254.0765; found 254.0759.

2,5-Dihydro-3-methylthiophene 1-oxide (32).[22]



A solution of isoprene **30** (0.42 mL, 4.20 mmol) and 1,2,3-trithia-phenalene 2-oxide **59** (100 mg, 0.42 mmol) in degassed chlorobenzene (50 cm^3) was refluxed for 6 h, until **59** was fully consumed. The solvent was removed under reduced pressure. The oily residue was dissolved in methanol (20 cm^3) and the solvent removed again. Purification by column chromatography was performed with 60-80 petroleum ether first, to yield [1,8-*c,d*]-1,2-dithiole **61** (90 mg, 100%). The column was then flushed with ethanol to yield **32** (36 mg, 74%) as a colourless oil; υ_{max} (CH_2Cl_2)/cm^{-1} 1087 (SO); δ_H(360 MHz; $CDCl_3$) 1.85 (3H, s, 6-H), 3.31-3.46 (2H, m, 2-H), 3.66-3.80 (2H, m, 5-H), 5.53 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 18.9 (q, 6-C), 62.20 (t, 2-C), 65.2 (t, 5-C), 121.4 (d, 4-C), 137.7 (s, 3-C); *m/z* (LREI) 116 (M^+; 100%), 99 (16), 85 (21), 68 (45), 67 (92), 53 (62).

3-(4'-Methyl-3'pentyl)-2,5-dihydrothiophene 1-oxide (46).[22]

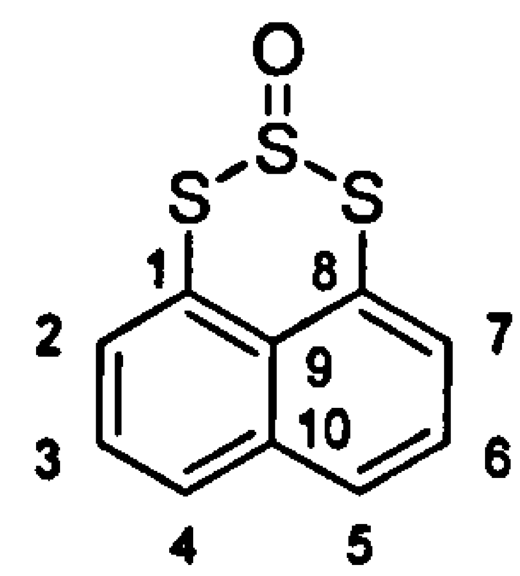


A solution of myrcene (0.18 cm^3, 1.05 mmol) and 1,2,3-trithia-phenalene 2-oxide **59** (100 mg, 0.42 mmol) in degassed chlorobenzene (50 cm^3) were heated at reflux for 6 h, until **59** was fully consumed. The solvent was removed under reduced pressure. The oily residue was dissolved in methanol (20 cm^3) and the solvent removed again. Purification by column chromatography was performed with 60-80 petroleum ether, to yield [1,8-*c,d*]-1,2-dithiole **61** (90 mg, 100%).

The column was then flushed with ethanol to yield **46** (72 mg, 93%) as an yellow oil; υ_{max} (CH_2Cl_2)/cm^{-1} 1032 (SO); δ_H(360 MHz; $CDCl_3$) 1.61 (3H, s, 10-H), 1.69 (3H, s, 11-H), 2.20-2.29 (4H, m, 6-H and 7-H), 3.43 (1H, d, *J* 17.0, 5-H_a or 5-H_b,), 3.52 (1H, s, 2-Ha or 2-

$H_{b'}$), 3.75 (1H, dd, *J* 17.0 and 1.2, 5-H_a or 5-$H_{b'}$), 3.84 (1H, d, *J* 17.0, 2-H_a or 2-$H_{b'}$), 5.09 (1H, bs, 8-H), 5.61 (1H, bs, 4-H); δ_C (90 MHz; $CDCl_3$) 18.1 (q, 10-C or 11-C), 26.1 (q, 10-C or 11-C), 26.7 (t, 6-C), 31.7 (t, 7-C), 60.1 (t, 2-C), 62.1 (t, 5-C), 118.4 (d, 4-C), 123.4 (d, 8-C), 133.0 (s, 9-C), 140.3 (s, 3-C); *m/z* (LREI) 184 (M^+; 24%), 135 (30), 121 (17), 116 (24), 93 (33), 69 (100); *m/z* (HREI) calcd for $C_{10}H_{16}SO$ 184.0922; found 184.0921.

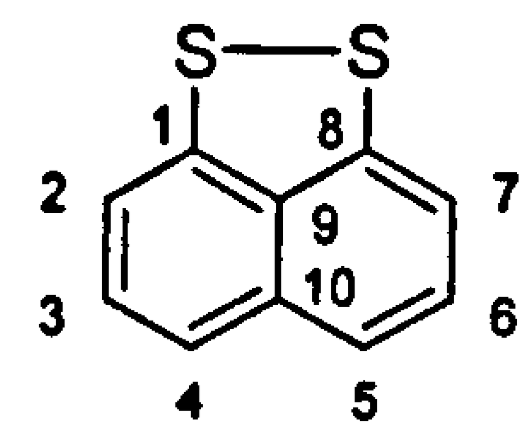
1,2,3-Trithia-phenalene 2-oxide (59)



A two neck, oven dried, 500 cm^3 round bottom flask equipped with a dropping funnel and a condenser were flushed with argon. Lithium aluminium hydride (150 mg, 3.84 mmol) was suspended in diethyl ether (30 cm^3). A solution of [1,8-*c,d*]-1,2-dithiole **61** (1.45 g, 7.63 mmol) in dry diethyl ether (100 cm^3) was added dropwise at room temperature over 30 minutes. The mixture was then heated at reflux for 60 minutes. After quenching with 10% H_2SO_4 (50 cm^3), the organic layer was separated and washed with brine. The aqueous layer was then extracted with dichloromethane (2 x 50 cm^3). The combined organic layers were then dried over $MgSO_4$ and the solvent was removed under reduced pressure. The white residue was then dissolved in diethyl ether (250 cm^3), the solution transferred into a dropping funnel and pyridine added (0.70 cm^3, 8.65 mmol). The mixture in the dropping funnel was then added dropwise to thionyl chloride (0.86 cm^3, 11.07 mmol) in diethyl ether (100 cm^3) at 0 °C over 30 minutes. Stirring was continued for a further 4 hours, allowing the reaction to reach room temperature. The reaction was quenched with 10% H_2SO_4 (20 cm^3) and the organic layer separated. The aqueous layer was washed with dichloromethane and the two combined organic portions washed with brine and dried over $MgSO_4$. Purification by column chromatography (50:50 60-80 petroleum ether:diethyl ether) gave **61** (570 mg, 39%) followed by **59** (1.096 g, 60%) as a yellow crystalline solid; R_f **(59)** 0.2 (70:30 petroleum ether: diethyl ether); υ_{max} (nujol)/cm^{-1} 1097 (SO); δ_H(360 MHz; $CDCl_3$) 7.56 (2H, t, *J* 7.5, 3-H and 6-H), 7.60 (2H, dd, *J* 7.5 and 1.5, 2-H and 7-H), 7.93 (2H, dd, *J* 7.5 and 1.5, 4-H and

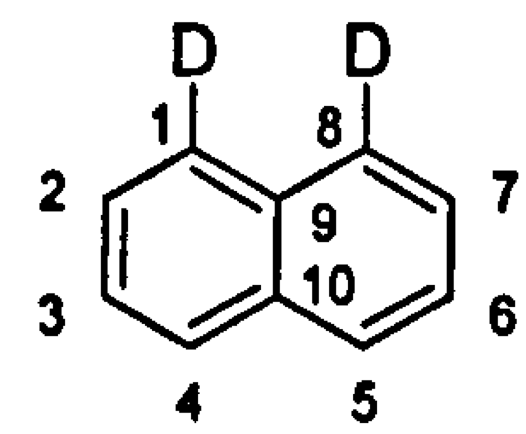
5-H); δ_C (90 MHz; $CDCl_3$) 122.2 (d, 4-C and 5-C), 124.2 (d, 3-C and 6-C), 126.8 (d, 2-C and 7-C), 131.3 (s, 10-C), 132.3 (s, 9-C) 134.9 (s, 1-C and 8-C); *m/z* (LREI) 208 (M^+; 44%), 134 (55), 106 (100), 102 (65), 76 (23), 51 (10); *m/z* (HREI) calcd for $C_{10}H_6S_3O$ 238.3368; found 238.3371.

[1,8-*c*,*d*]-1,2-Dithiole (61)



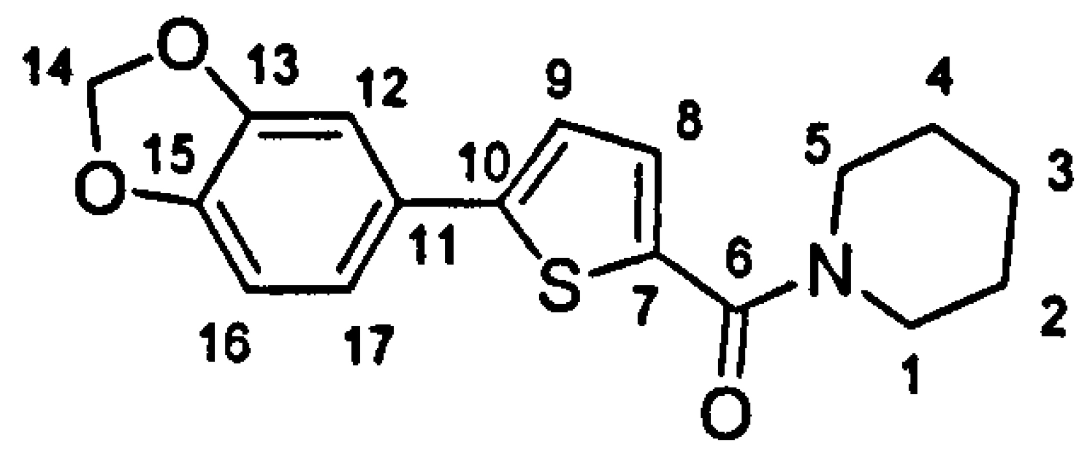
A 500 cm^3 oven-dried three-neck round bottom flask was equipped with a magnetic stirrer, a condenser and a nitrogen inlet. Butyllithium (2.07 M in hexane, 30 cm^3, 62.50 mmol) was syringed in the flask and diluted with freshly distilled diethyl ether (150 cm^3). The solution was cooled to –20 °C and 1-bromonaphthalene **83** (8.75 cm^3, 62.50 mmol) was added dropwise over 5 minutes. The mixture was stirred for 15 minutes and the temperature allowed to reach 10 °C. The mixture was then cooled to –20 °C, stirring was interrupted and the supernatant liquid was removed *via* cannula, leaving a white solid. Fresh diethyl ether (30 cm^3) was then introduced. Stirring was recommenced, the mixture allowed to reach –10 °C and after 10 minutes cooled to –20 °C; stirring was interrupted and the liquid removed *via* cannula. This procedure was repeated two more times. After removing the liquid for the third time, a mixture of butyllithium (2.07 M in hexane, 30 cm^3, 62.50 mmol) and N,N,N',N'-tetramethylethylenediamine (9.80 cm^3, 62.50 mmol) was added to the solid at –10 °C and the reaction allowed to reach room temperature. The mixture was then refluxed for 4 hours (until disappearance of white fumes) and then cooled down to room temperature. The oil bath was then replaced with an acetone bath and the mixture was cooled to –78 °C. The supernatant solution was removed *via* cannula. The solid residue was diluted with tetrahydrofuran (30 cm^3), S_8 added (4g, 62.50 mmol) and the reaction stirred overnight (15 hours), warming to room temperature. The mixture was then diluted with dichloromethane and portions of 1g of triphenylphosphine were added until disappearance of S_8 (TLC). The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-80 petroleum ether) to afford **61** (3.584 g, 31%) as an orange crystalline solid. For spectroscopic data refer to page 21.

1,8-*d*-Naphthalene (86).[46]



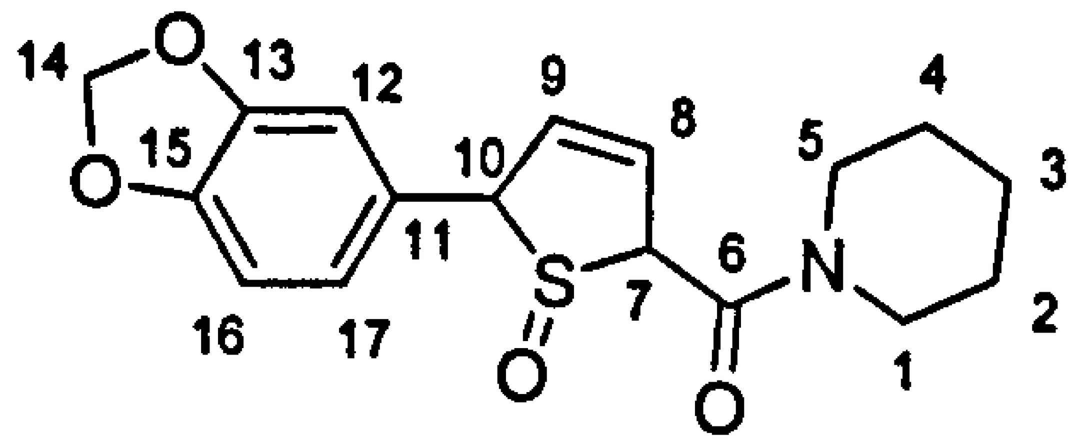
A 500 cm^3 oven-dried three-neck round bottom flask was equipped with a magnetic stirrer, a condenser and a nitrogen inlet. Butyllithium (2.07 M in hexane, 6 cm^3, 12.50 mmol) was syringed into the flask and diluted with freshly distilled diethyl ether (50 cm^3). The solution was cooled to –20 °C and 1-bromonaphthalene **83** (1.75 cm^3, 12.50 mmol) was added dropwise over 5 minutes. The mixture was stirred for 15 minutes and the temperature allowed to reach 10 °C. The mixture was then cooled to –20 °C, stirring was interrupted and the supernatant liquid was removed *via* cannula, leaving a white solid. Fresh diethyl ether (20 cm^3) was then introduced. Stirring was recommenced, the mixture allowed to reach –10 °C and after 10 minutes cooled to –20 °C; stirring was interrupted and the liquid removed *via* cannula. This procedure was repeated two more times. After removing the liquid for the third time, a mixture of butyllithium (2.07 M in hexane, 6.5 cm^3, 13.45 mmol) and *N,N,N',N'*-tetramethylethylenediamine (2.63 cm^3, 17.50 mmol) was added to the solid at –10 °C and the reaction allowed to reach room temperature. The mixture was then refluxed for 3 hours (until disappearance of white fumes) and then cooled down to room temperature. The oil bath was then removed and the temperature of the mixture was increased to room temperature. D_2O Was added (2 cm^3, 100 mmol) and the reaction was stirred for 1 hour. The organic layer was separated and the aqueous layer washed with diethyl ether (3x50 cm^3). The combined organic layers were then dried over $MgSO_4$ and removed *in vacuo*. The residue was purified by recrystallization (70:30 methanol:H_2O) to afford **86** (5.70 g, 36%) as a pale yellow crystalline solid; δ_H(360 MHz; $CDCl_3$) 7.15 (2H, d, *J* 8.1, 4-H and 5-H), 7.27 (2H, dd, *J* 8.1 and 7.4, 3-H and 6-H),7.35 (2H, d, *J* 7.4, 2-H and 7-H); δ_C(100 MHz, $CDCl_3$) 126.1, 126.2, 127.9, 128.3, 133.7, 133.8; *m/z* (LREI) 130 (M^+ 100%), 129 (63), 128 (15), 65 (8).

(5-Benzo[1,3]dioxol-5-yl-thiophen-2-yl)piperidin-1-yl-methanone (108)



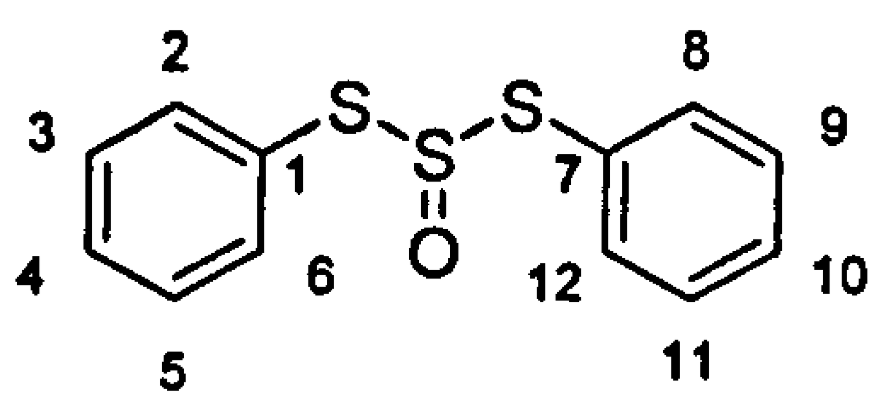
A solution of piperine **106** (1.1 g, 3.85 mmol) and 1,2,3-trithia-phenalene 2-oxide **59** (300 mg, 1.26 mmol) in degassed chlorobenzene (50 cm^3) was refluxed for 16 h, until disappearance of **59** (TLC). The solvent was removed under reduced pressure. The oily residue was dissolved in methanol (20 cm^3) and the solvent removed again. Purification by column chromatography was performed with petroleum ether first, to yield [1,8-*c*,*d*]-1,2-dithiole **61** (230 mg, 96%). The column was then eluted with 60:40 60-80 petroleum ether:diethyl ether to yield first **108** (90 mg, 23%) as a white crystalline solid; R_f 0.2 (50:50 60-80 petroleum ether:diethyl ether); υ_{max} (nujol)/cm^{-1} 1606 (C=O); δ_H(500 MHz; $CDCl_3$) 1.64-1.72 (6H, m, 2-H, 3-H and 4-H), 3.69-3.72 (4H, m 1-H and 5-H), 6.00 (2H, s, 14-H), 6.83 (1H, d, *J* 8.1, 16-H), 7.08-7.09 (2H, m, 9-H and 12-H), 7.11 (1H, dd, *J* 8.1 and 1.8, 17-H), 7.21 (1H, d, *J* 3.8, 8-H); δ_C (90 MHz; $CDCl_3$) 25.0 (t, 3-C), 26.6 (t, 2-C and 4-C), 46.6 (b) (1-C and 5-C),101.8 (t, 14-C), 107.0 (d, 8-C or 9-C), 109.1 (d, 8-C or 9-C), 120.4, 122.2, 129.9 (d, 12-C, 16-C and 17-C), 128.3 (s, 10-C), 136.2 (s, 7-C), 147.5, 148.2, 148.6 (s, 11-C, 13-C and 15-C), 163.6 (s, 6-C); *m/z* (LREI) 315 (M^+; 4%), 285 (76), 201 (91), 173 (60), 143 (46), 115 (100), 100 (14); *m/z* (HREI) calcd for $C_{17}H_{17}O_3NS$ 315.0929; found 315.0883.

Chromatography subsequently also yielded another product, possibly sulfoxide **107** (105 mg, 30%) as a yellowish oil;



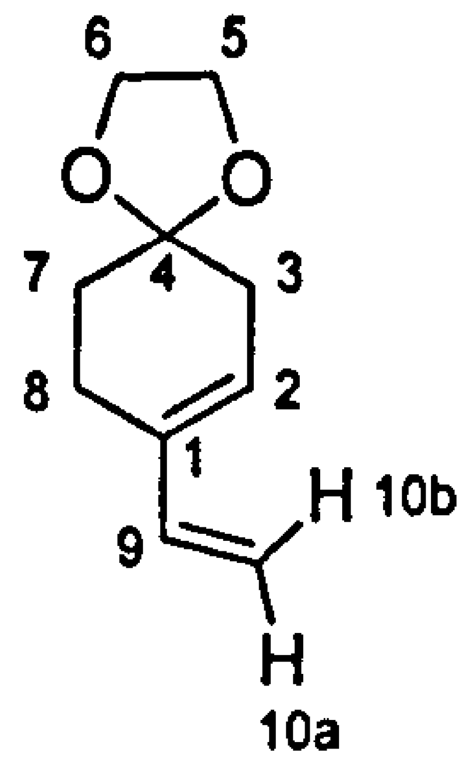
R_f 0.15 (50:50 petroleum ether: diethyl ether); υ_{max} (nujol)/cm^{-1} 1606 (C=O), 1038 (S=O); δ_H(360 MHz; $CDCl_3$) 1.55-1.58 (6H, m, 2-H, 3-H and 4-H), 3.46-3.65 (4H, m, 1-H and 5-H), 5.95-6.00 (3H, m, 7-H and 14-H), 6.50 (1H, t, *J* 11.1, 8-H), 6.62 (1H, d, *J* 15.6, 10-H), 6.76 (1H, d, *J* 8.1, 16-H), 6.90 (1H, dd, *J* 8.1 and 1.7, 17-H), 7.03 (1H, d, *J* 1.7, 12-H), 7.43 (1H, ddd, *J* 15.7, 11.1 and 1, 9-H); δ_C (90 MHz; $CDCl_3$) 25.0, 26.1, 27.1 (t, 1-C to 5-C), 101.6 (t, 14-C), 106.3, 108.7 (d, 7-C and 10-C), 120.3, 122.8, 124.0, (d, 12-C, 16-C and 17-C), 131.4 (s, 11-C), 138.0, 138.6 (d, 8-C and 9-C), 148.4, 148.2, (s, 13-C and 15-C), 166.1 (s, 6-C); *m/z* (LREI) 333 (M^+; 2%), 315 (100), 285 (17), 267 (28), 232 (38), 204 (76), 159 (65); *m/z* (HREI) calcd for $C_{17}H_{19}O_4NS$ 333.1035; found 332.9823.

1,3-diphenyl-trisulfide 2-oxide (109).[41]



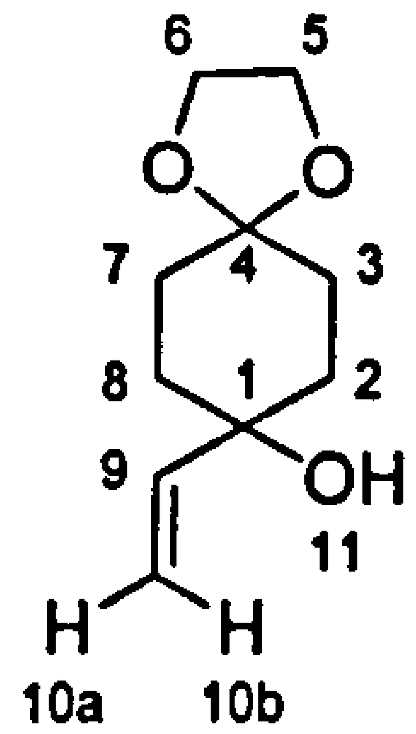
A two necked, oven dried, 250 cm^3 round bottom flask was flushed with argon and charged with thionyl chloride (0.280 cm^3, 3.78 mmol) in diethyl ether (50 cm^3); this solution was then cooled down to 0 °C. A mixture of thiophenol (0.80 cm^3, 7.58 mmol) and pyridine (0.560 cm^3, 7.58 mmol) in dry diethyl ether (100 cm^3) was added dropwise over 30 minutes. After quenching with water, the organic layer was separated and washed with brine, 3M aqueous NaOH and water. The aqueous layer was then washed with dichloromethane (2 x 50 cm^3) and the two combined organic portions washed with brine and dried over $MgSO_4$ to give **109** (1.150 g, 100%) as a yellow oil; υ_{max} (nujol)/cm^{-1} 1120 (SO); δ_H(360 MHz; $CDCl_3$) 7.27-7.77 (10H, m, 2-H to 12-H); δ_C (90 MHz; $CDCl_3$) 128.1, 128.6, 130.5 (d, 2-C to 6-C and 8-C to 12-C), 136.5 (s, 1-C and 7-C); *m/z* (LREI) 266 (M^+; 15%), 250 (54), 218 (99), 154 (42), 109 (100), 65 (60).

8-Vinyl-1,4-dioxa-spiro[4.5]dec-7-ene (118).[60]



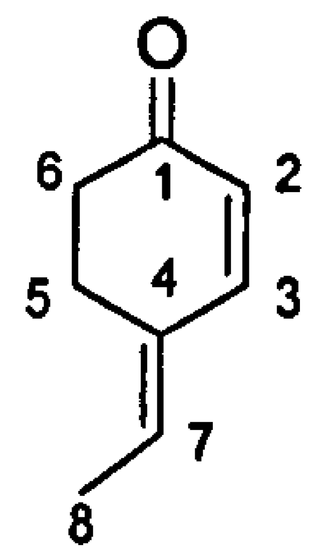
Alcohol **121** (4.53 g, 24.61 mmol) was dissolved in freshly distilled toluene (150 cm^3) in a 500 cm^3 round bottom flask. Molecular sieves (5 Å, 100 g) were added and stirring started under an argon atmosphere. *p*-Toluenesufonic acid (1g, 5.26 mmol) was added in one portion. Stirring was continued for 5 days, adding daily portions of 1 gram of *p*-toluenesufonic acid. The sieves were removed by filtration, washed with diethyl ether and the solution washed with saturated aqueous sodium bicarbonate. The organic layer was separated and the acqueous layer washed with diethyl ether. The combined organic layers were then dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (80:20 60-80 petroleum ether:ethyl acetate) gave (1.38 g, 34%) of **118** as a colourless oil; R_f 0.70 (80:20 60-80 petroleum ether:ethyl acetate); υ_{max} (CH_2Cl_2)/cm^{-1} 1652 (C=C); δ_H(400 MHz; $CDCl_3$) 1.75 (2H, m, 7-H), 2.29-2.32 (4H, m, 3-H and 8-H), 3.91 (4H, s, 5-H and 6-H), 4.87 (1H, d, *J* 10.7, 10-H_a), 5.02 (1H, d, *J* 17.5, 10-H_b), 5.57 (1H, dd, *J* 3.8 and 3.4, 2-H), 6.29 (1H, dd, *J* 17.5 and 10.7, 9-H); δ_C (100 MHz; $CDCl_3$) 21.4 (t, 7-C), 31.1 (t, 3-C or 8-C), 36.5 (t, 3-C or 8-C), 64.7 (t, 5-C or 6-C), 64.8 (t, 5-C or 6-C), 109.4 (s, 4-C), 111.5 (t, 10-C), 126.5 (d, 2-C), 135.9 (s, 1-C), 139.2 (d, 9-C); *m/z* (LREI) 166 (M^+; 10%), 157 (18), 143 (100), 129 (11), 105 (12), 99 (14).

8-Vinyl-1,4-dioxa-spiro[4.5]decan-8-ol (121).[60]



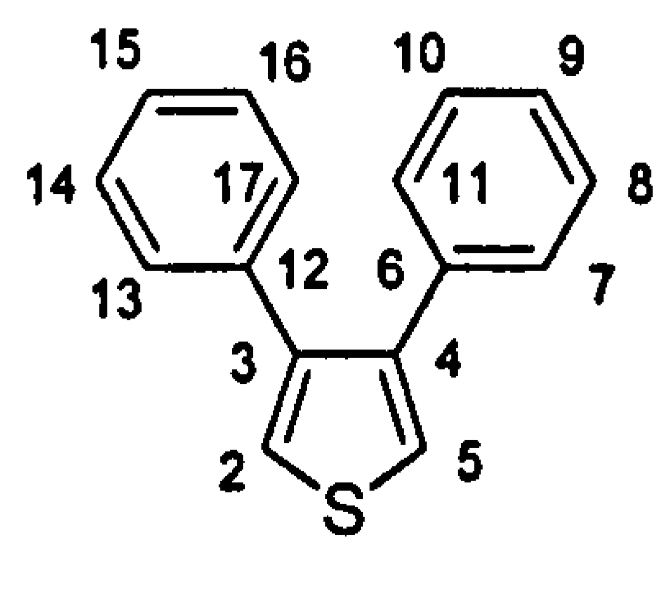
A two necked, oven dried, 250 cm^3 round bottom flask equipped with a dropping funnel was flushed with argon. Vinylmagnesium bromide solution in tetrahydrofuran (1M, 30 cm^3, 30.00 mmol) was diluted with freshly distilled tetrahydrofuran (50 cm^3). A solution of 1,4-cyclohexanedione monoethylene ketal **119** (4.51 g, 30.0 mmol) in THF was added dropwise at room temperature over 30 minutes. After completion of the addition the mixture was stirred overnight. The reaction was quenched with 10% HCl until neutrality and diluted with diethyl ether. The solvents were then removed *in vacuo* and the residue was re-dissolved in diethyl ether and washed sequentially with 3% HCl, saturated aqueous sodium bicarbonate and brine. The solution was then dried over $MgSO_4$ and the solvent removed *in vacuo* to give **121** (4.72 g, 89%) as a pale yellow oil of satisfactory purity to carry out the subsequent reaction. R_f 0.25 (50:50 60-80 petroleum ether: ethyl acetate); υ_{max} (CH_2Cl_2)/cm^{-1} 3738 (O-H), 1020 (C-O); δ_H(400 MHz; $CDCl_3$) 1.32 (1H, s, 11-H), 1.66-2.02 (8H, m, 2-H, 3-H, 7-H and 8-H), 3.95, 3.96 (4H, d, *J* 3.5, 5-H and 6-H), 5.07 (1H, dd, *J* 10.7 and 1.1, 10-H_a), 5.29 (1H, dd, *J* 17.4 and 1.1, 10-H_b), 5.99 (1H, dd, *J* 17.4 and 10.7, 9-H); δ_C (100 MHz; $CDCl_3$) 30.7, 35.3, 37.3, 37.4 (t, 2-C, 3-C, 7-C and 8-C), 64.6 (t, 5-C and 6-C), 71.3 (s, 1-C), 108.9 (s, 4-C), 112.3 (t, 10-C), 145.7 (d, 9-C); *m/z* (LREI) 184 (M^+; 1%), 124 (10), 101 (42), 99 (100), 86 (91), 55 (86); *m/z* (HREI) calcd for $C_{10}H_{16}O_3$ 184.1099; found 184.1100.

4-Vinyl-cyclohex-3-enone (122).[68]



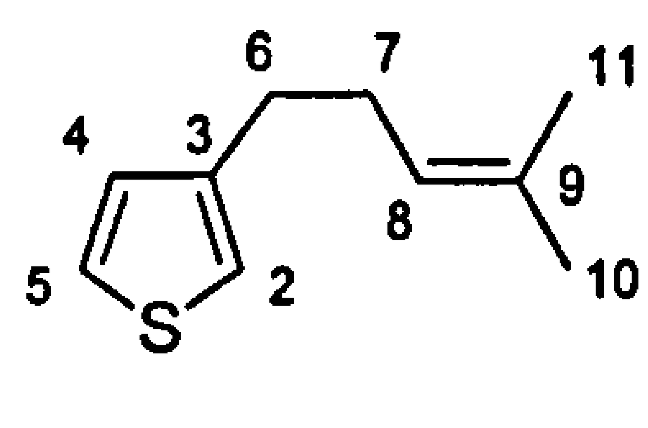
A solution of diene **118** (626 mg, 3.15 mmol) and 1,2,3-trithia-phenalene 2-oxide **59** (300 mg, 1.26 mmol) in degassed chlorobenzene (50 cm^3) was refluxed for 4 h. The solvent was removed under reduced pressure. The oily residue was dissolved in methanol (20 cm^3) and the solvent removed again. Purification by column chromatography was performed with 60-80 petrol ether first, to yield [1,8-*c*,*d*]-1,2-dithiole **61** (180 mg, 75%). The column was then eluted with 90:10 60-80 petroleum ether:ethyl acetate to yield **59** (75 mg, 25%) and then ketone **122** (150 mg, 25%-based on diene) as a yellow oil; R_f 0.2 (80:20 60-80 petroleum ether:ethyl acetate); υ_{max} (nujol)/cm^{-1} 1656 (CO), 844; δ_H(500 MHz; $CDCl_3$) 1.84 (3H, d, *J* 7.1, 8-H), 2.49-2.52 (2H, m, 6-H), 2.66-2.73 (2H, m, 5-H), 5.85 (1H, d, *J* 9.8, 2-H), 5.92-5.97 (1H, m, 7-H), 7.00 (1H, d, *J* 9.8, 3-H); δ_C (100 MHz; $CDC1_3$) 14.0 (s, 8-C), 23.8 (s, 5-C), 36.3 (s, 6-C), 124.8 (s, 2-C, 132.4 (s, 7-C), 133.3(s, 4-C), 149.4 (s, 3-C), 199.5 (s, 1-C); *m/z* (LREI) 122 (M^+; 100%), 107 (28), 95 (40), 79 (77), 66 (29), 51 (17), 39 (29).

3,4-diphenyl-thiophene (138).[69]



In a round bottom flask equipped with a reflux condenser, 3,4-diphenyl-2,5-dihydro-thiophene **14** (130 mg, 0.51 mmol) was dissolved in acetic anhydride (20 cm^3) and refluxed for 3 hours. The majority of the solvent was removed *in vacuo*, the residue was diluted with dichloromethane and washed with saturated aqueous $NaHCO_3$ (2 x 50 cm^3). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (60-80 petroleum ether) yielded **138** (75 mg, 63%) as a white crystalline solid. R_f 0.2 (60-80 petroleum ether); δ_H(500 MHz; $CDCl_3$) 7.10-7.20 (12H, m, 2-H to 17-H); δ_C (90 MHz; $CDCl_3$) 124.4 (d, 2-C and 5-C), 127.3, 128.5, 129.4 (d, 7-C to 11-C and 13-C to 17-C), 136.9 (s, 3-C and 4-C), 142.1 (s, 6-C and 12-C); *m/z* (LREI) 236 (M^+; 100%), 221 (15), 202 (8), 189 (13), 163 (3), 89 (5).

3-(4-Methyl-pent-3-enyl)-thiophene (139).[67]



In a round bottom flask equipped with a reflux condenser, **46** (122 mg, 0.66 mmol) was dissolved in acetic anhydride (20 cm^3) and refluxed for 2 hours. The majority of the solvent was removed *in vacuo*, the residue was diluted with dichloromethane and washed with saturated aqueous $NaHCO_3$ (2x50 cm^3). The combined organic layers were then dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (50:50 60-80 petroleum ether:diethyl ether) yielded **139** (56 mg, 50%) as a yellow oil. R_f 0.4 (50:50 60-80 petroleum ether:diethyl ether); δ_H(360 MHz; $CDCl_3$) 1.49 (3H, s, 10-H), 1.60 (3H, d, *J* 0.9, 11-H), 2.18-2.25 (2H, m, 7-H), 2.57 (2H, t, *J* 7.3, 6-H), 5.05-5.15 (1H, m, 8-H), 6.85 (1H, d, *J* 3.0, 2-H), 6.86 (1H, d, *J* 4.8, 4-H), 7.14 (1H, dd, *J* 4.8 and 3.0 Hz, 5-H); *m/z* (LREI) 236 (M^+; 100%), 221 (15), 202 (8), 189 (13), 163 (3), 89 (5).

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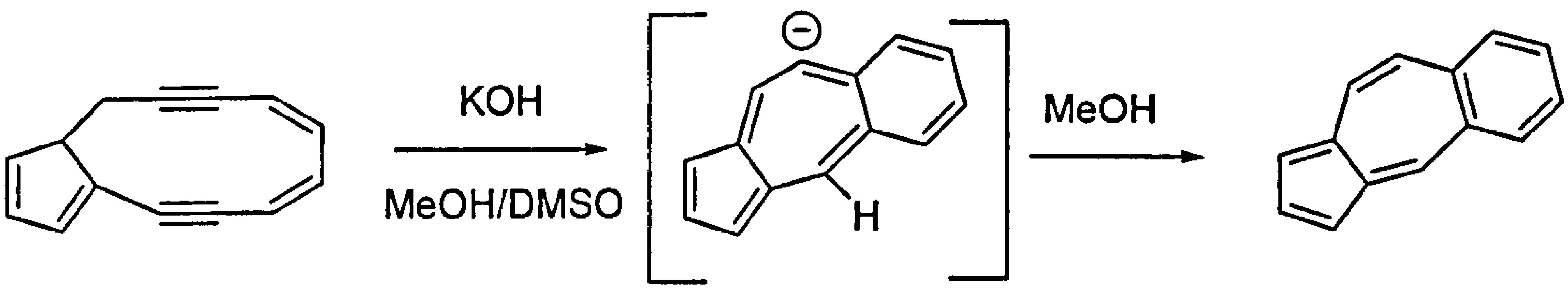
CHAPTER III:

Synthesis, Characterization and Reactivity of Novel Sulfur-Containing Cyclic Enediynes

BACKGROUND AND SIGNIFICANCE

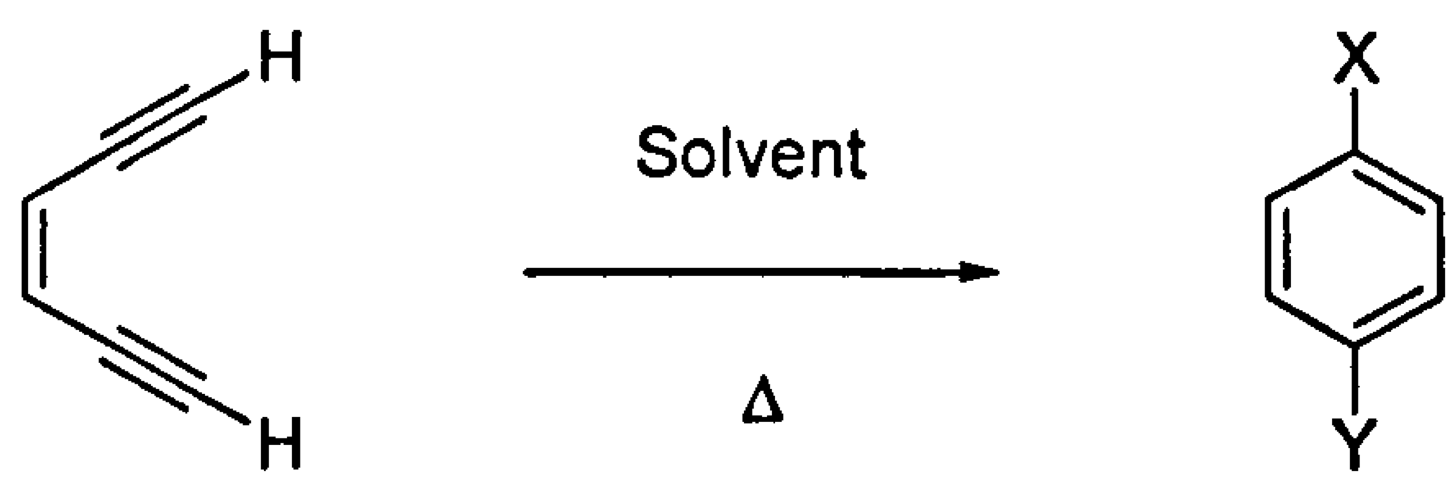
3.1.1. The Enediyne System.

The chemistry of enediynes dates back to the mid-1960's. The first paper on the subject, by Sondheimer, was published in 1966 and reported the reaction shown in Scheme 3.1.[1] An ionic mechanism was proposed for the observed cyclisation.



Scheme 3.1

Bergman published the first in-depth study on the thermal behaviour of such systems in 1972,[2] where simple acylic (*Z*)-enediynes were chosen as model compounds. For instance, when enediyne **1** was heated in solution, benzene or its derivatives **2** were the observed products, depending on the solvent used (Scheme 3.2).

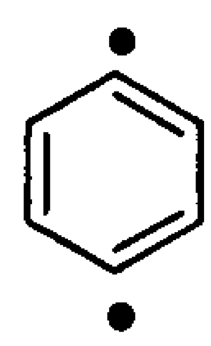


1 **2**

Solvent	X	Y
Hydrocarbon	H	H
CCl_4	Cl	Cl
CH_3OH	CH_2OH	H

Scheme 3.2

To account for such an outcome, the author postulated the intermediacy of the highly unstable 1,4-dehydrobenzene **3**, which abstracts hydrogen and/or other species from the solvent;[3] hereafter the cycloaromatisation of enediynes via biradicals is known as the "Bergman cyclisation".[4]



3

Figure 3.1

Such a peculiar feature in the reaction mechanism was enough to attract the interest of both theoretical and synthetic chemists. Moreover, the discovery of two naturally occurring antitumor antibiotics, esperamicin A_{1B} **4**[5] and calicheamicin γ_1' **5**[6] (Figure 3.2) marked a milestone in the design of a new class of chemotherapeutic agents; in these systems the fascinating mechanism of action of enediynes was playing a pivotal role.

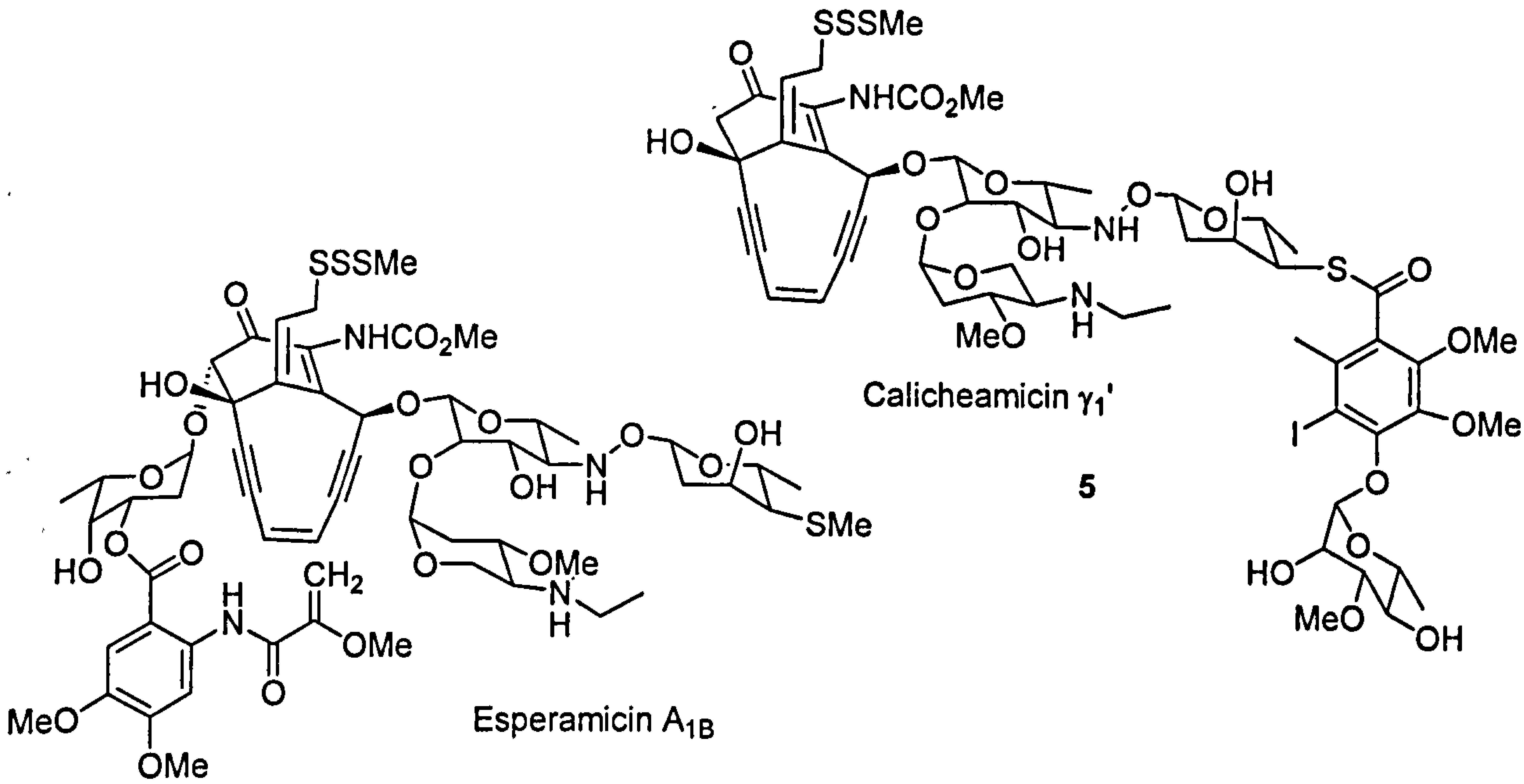
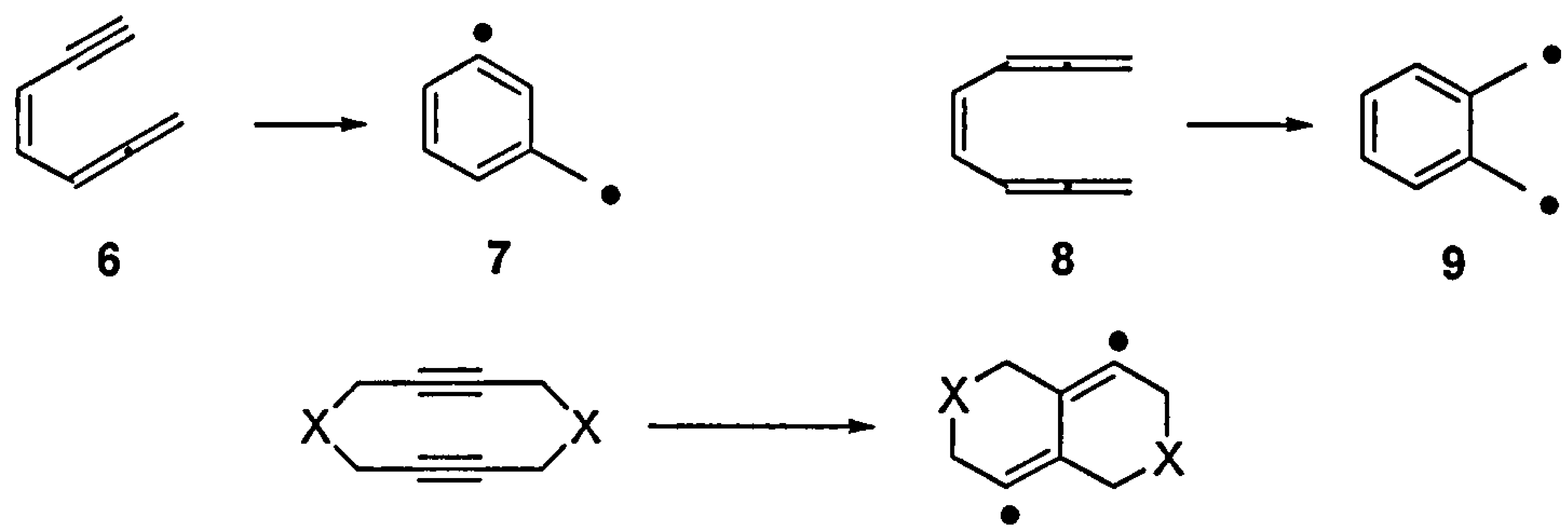


Figure 3.2

Calicheamicin γ_1 and esperamicin A_{1B} contain a bicyclic bridged enediyne structure that cyclise to biradicals that in turn can cleave DNA double strand, with a similar mechanism as the systems studied by Bergman. Prompted by these revelations, chemists succeeded in synthesising alternative unsaturated structures that could cyclise to give biradical species.

Several have been discovered, some of which show promising DNA cleavage activity (Scheme 3.3).[7]

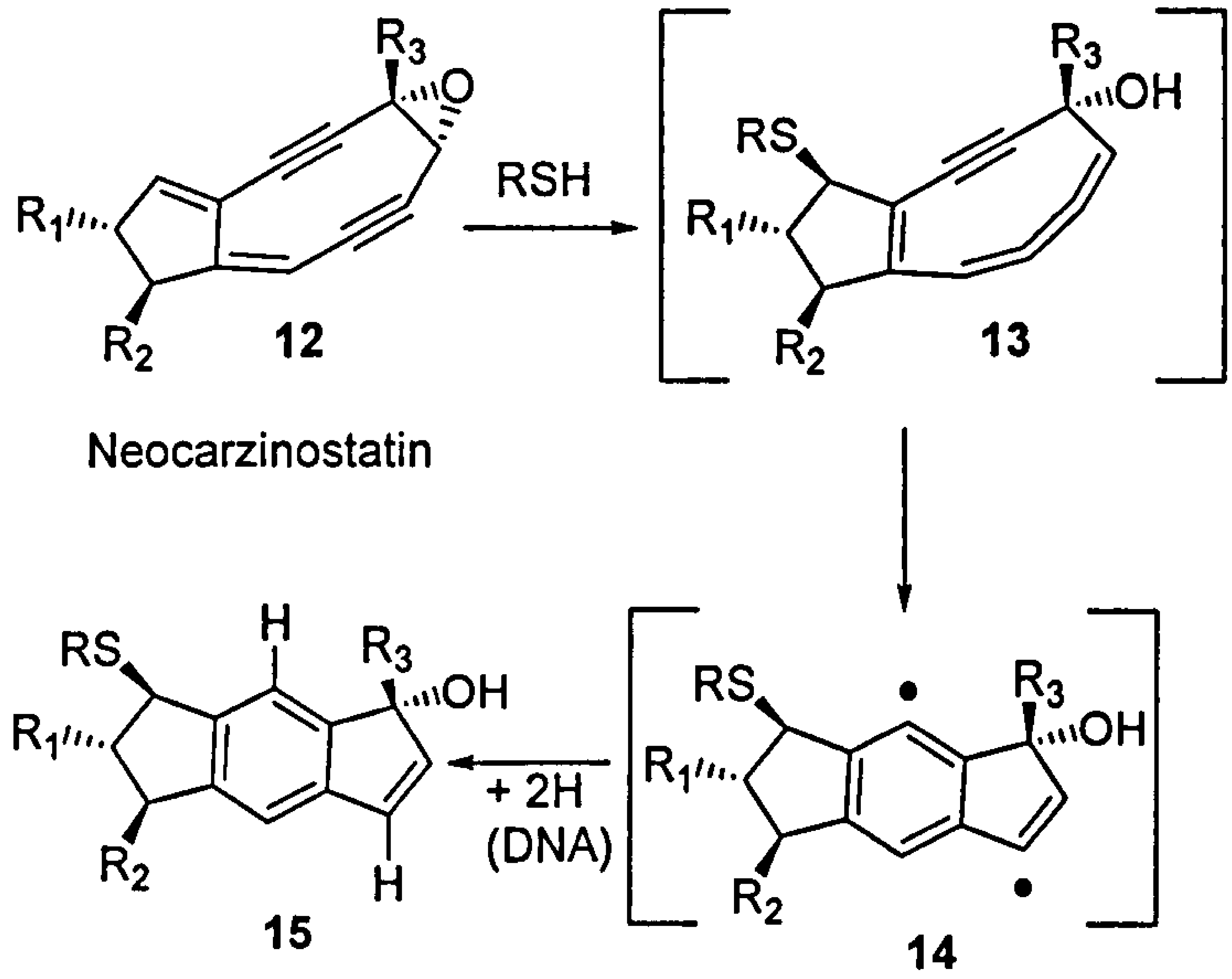


6 7 8 9

10 11

Scheme 3.3

Further investigations on the subject brought to light a whole range of naturally occurring enediynes. These are now divided in three families, namely, (1) the calicheamicins/esperamicins family possessing an enediyne chromophore with a methyl trisulfide group, (2) the dynemicin family, where the enediyne unit is associated with the hydroxyanthraquinone chromophore and (3) the chromoprotein family, which consist of nonpeptidic chromophore such as kedarcidin, C-1027 or neocarzinostatin complexed with an apoprotein that acts as a carrier. Detailed studies on their mechanism of action have been published.[8] Most of these products possess an enediyne unit as part of an overall structure that also contains a DNA-binding moiety (a glycosylated aminosugar or an intercalating structure). They act as prodrugs that can be metabolised by thiols into active biradicals; the latter break the DNA double helix by damaging its sugar phosphate backbone. For instance, in Scheme 3.4, the mechanism of biological activity of neocarzinostatin is shown.[9] Strictly speaking, this molecule does not belong to the same family in that it does not possess a conjugated enediyne unit; nevertheless, once activated, it acts in the same way.



Scheme 3.4

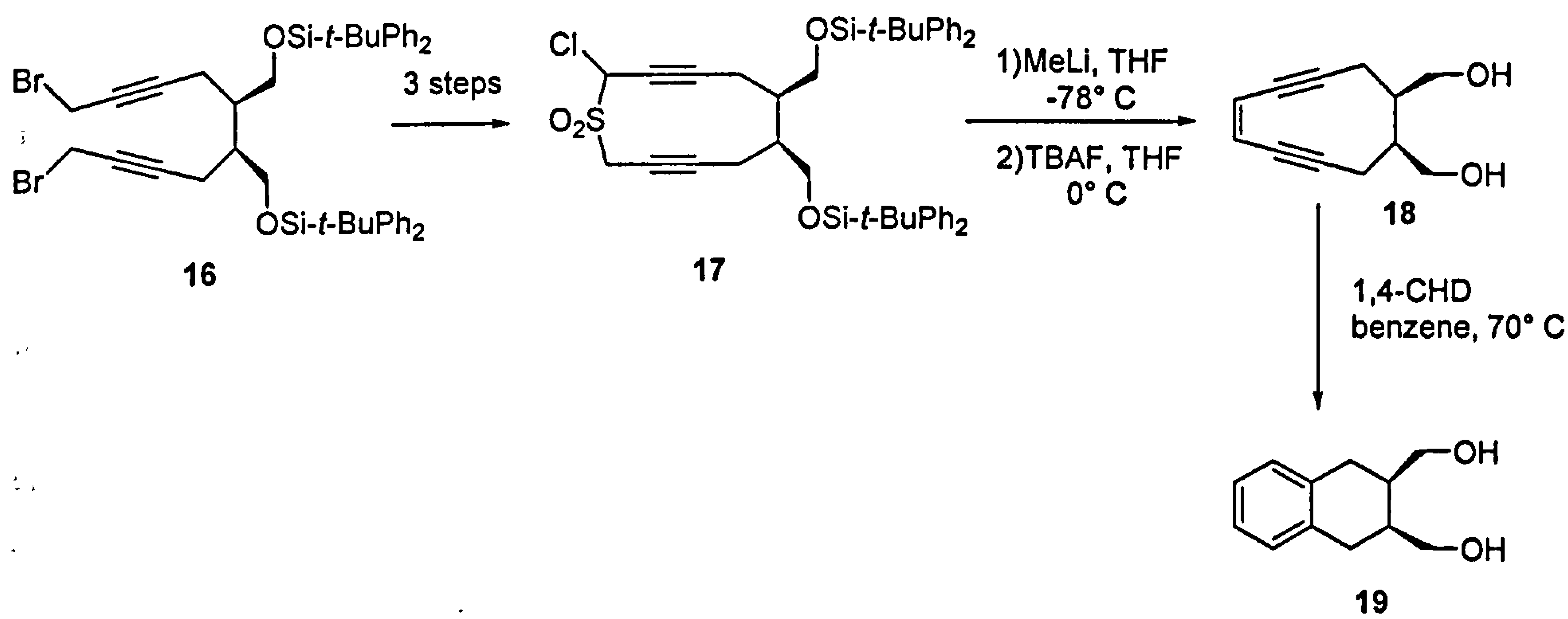
The cycloaromatisation of the nonprotein chromophore NCS-chrom **12** is triggered by the nucleophilic addition of a thiol, giving an indacene biradical **14**; the subsequent abstraction of hydrogen from DNA leads to its cleavage. The complete process leaves an inactive form of the drug, devoid of further redox properties.

The majority of these molecules were isolated from the fermentation broth of different *sporae*.[8] However, total synthesis of some has been achieved (e.g. calicheamicin γ_1).[10] Although they have attracted much attention from a synthetic point of view, enediyne natural products have found limited use as therapeutic agents, owing to their toxicity and instability. Organic chemist have therefore sought to develop analogues and models of enediyne natural products that are more selective and stable and still retain or even exceed the efficacy of their natural counterparts. Nicolaou[11] listed several ideal characteristics of enediyne analogues that would allow such compounds to be clinically useful agents:

1. chemically stable under physiological conditions, yet able to undergo cyclisation upon suitable activation;
2. structurally simple, thus easily synthesised;
3. attachable to appropriate delivery systems through proper functionality;
4. equipped with suitable initiators that may be activated under mild biological conditions.

At the beginning the strategy, the synthesis of enediyne mimics had followed a common motif: the assembly a of 10-membered ring enediyne with a specific structural feature that precludes the cycloaromatisation at physiological conditions. The subsequent removal of the blocking device, by physical or chemical means, initiates the reaction and the formation of the aimed biradical. Several examples in the wake of this route have been reported.[10a,b;12]

At the same time, researchers have devoted time to the study of alternative cyclic enediynes in an effort to improve their DNA-damaging activity. Nicolaou and co-workers have designed a general pathway for the synthesis of monocyclic enediynes, employing the Ramberg-Backlund reaction as the key process to install the ene unit.[13] The water-soluble enediyne **18** cycloaromatised at and above 37° C to form **19**, causing at the same time cleavage of double stranded DNA in the absence of any additives (Scheme 3.5). Along with numerous papers devoted to the synthesis of enediynes, much research has been carried out on their reactivity and mechanism of action.



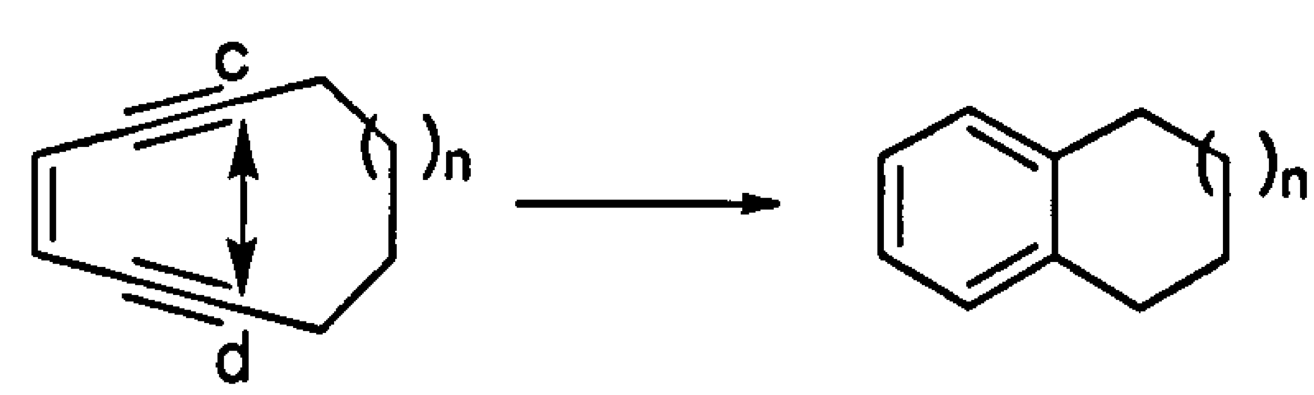
Scheme 3.5

3.1.2. The Bergman Cycloaromatisation: Mechanism.

It is generally accepted that the intermediacy of biradicals postulated by Bergman is a correct assumption; however, despite a large amount of indirect evidence, there is no direct proof of the existence of biradicals (Figure 3.1). On the contrary, there have been studies that tend to challenge such a theory. Lindh showed that, in natural products, the reduction in distance between the acetylenic termini during the activation (*vide infra*) is not sufficient to account for the observed rate of reaction *via* a 1,4-dehydroarene.[14] The author suggested instead a simultaneous ring closure and hydrogen abstraction mechanism. Calculations by Kraka and Cramer indicated that the transition state in the cyclisation of (*Z*)-hex-3-ene-1,5-diyne does not possess significant biradical character, although its geometry resembles that of a biradical.[15] It is now believed that the biradicals in the Bergman cyclisation form only in the singlet state, and that the intersystem crossing to the triplet state is much slower than the hydrogen abstraction. Attempts to increase the intersystem crossing by means of an external magnetic field or by using heavy atom solvents proved unsuccessful.[16] This may support the view that discrete 1,4-dehydroarenes do not exist. On the other hand, published data tend to support the correctness of Bergman's postulation: the heat of formation of 1,4-dehydroarenes radicals has been determined experimentally, giving values that match those obtained computationally.[15,17] Several other indirect proofs of the existence of a biradical intermediate have been reported, including reactions with radical trapping agent TEMPO[18] and many others radical acceptors.[19]

3.1.3. The Bergman Cycloaromatisation: Reactivity.

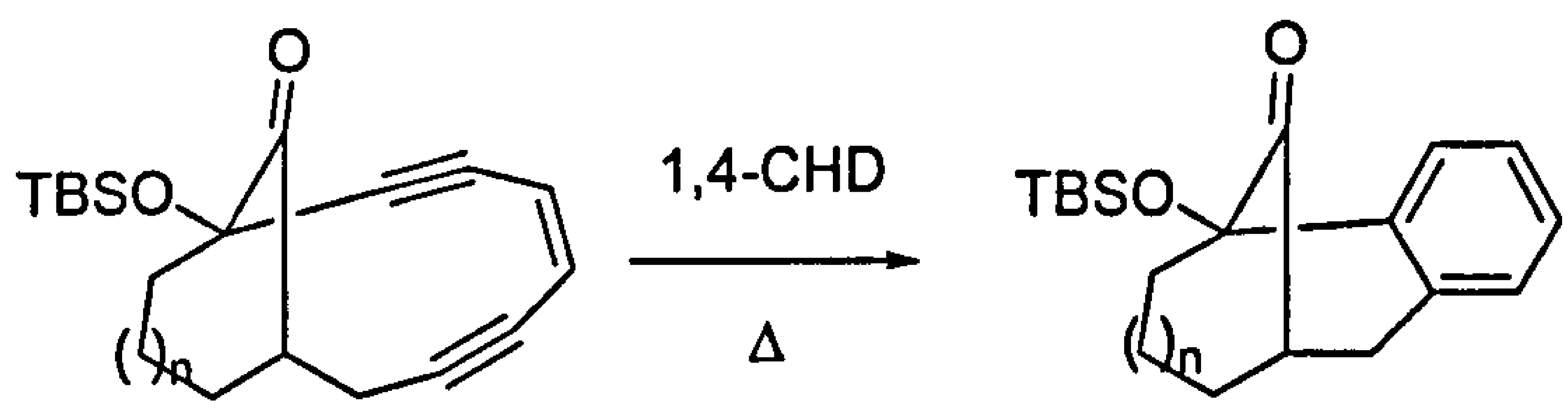
The reactivity of enediyne systems towards cyclisation is influenced by several factors. Among these the nature of the solvent,[20] concentration of the trapping agent[21] and the effect of substituents[22] can be listed. However, two major factors have been proposed to account for the likeliness of the cycloaromatisation to occur. One proposal is that the key cause for the cycloaromatisation to occur is related to the distance between the two terminal acetylenic carbons. Nicolaou and co-workers, for instance, prepared a series of relatively strain-free enediynes **20** (Scheme 3.6).[23] The cyclic enediynes with n=2 to n=7 were found to be stable at room temperature. In contrast cyclodec-3-ene-1,5-diyne (n=1) underwent spontaneous cyclisation.



20 **21**

Scheme 3.6

A general trend that related the ease of cyclisation with the shortening of the *cd* distance was noted (see Scheme 3.6). Following these observations, the author proposed that the upper limit for the *cd* distance before spontaneous cyclisation at room temperature occurs is around 3.2-3.3 Å. Other authors, using *ab initio* methods, obtained results that support the work by Nicolaou.[15] These observations seemed to be empirical and would apply only to very simple systems. The situation proved to be somewhat more complicated in by- and polycyclic enediynes. Independent studies by Snyder and Magnus gave strong evidence that the reactivity of strained enediynes is rather related to the difference in strain energy between transition and ground state.[24] Magnus, studying the systems in Scheme 3.7, reported that although **22** and **23** have similar *cd* distances, the latter cyclises faster at 71 °C than the former at 124 °C, in the presence of a proton donor such as 1,4-cyclohexadiene.[25]



22 n=0
23 n=1

24 n=0
25 n=1

Scheme 3.7

Snyder both measured and calculated (with a modified MM2 force-field) the energy barrier (ΔE*) between transition state [E(TS)] and ground state [E(GS)] for **22** and **23**. The measured values (ΔG*) are 110 kJ mol^{-1} and 131 kJ mol^{-1}, respectively (ΔΔE*=21 kJ mol^{-1}); the data obtained from the calculations showed similar values (ΔΔE*=24 kJ mol^{-1}).[26] The activation barrier for **22** is smaller because in the ground state the six-membered ring must adopt a quite strained boat conformation, which means a high-lying ground state. The method was indeed accurate but rather sophisticated.

Instead, two other models have been developed to predict the relative reactivity of different enediynes; either taking into account only the energy of the biradical intermediate,[25] or considering the energy of the ground states as well.[26] Both models, however, were based on two assumptions: the first is that if the transition state is product-like,[27] one can presume the energy of the biradical to be the same to that of the transition state. The second is that the enthalpy of the C-H formation is basically independent of the structure of the biradical.[28] This meant that calculations were performed on the product, after hydrogen abstraction. Corroborated by the work of other authors, a general rule was proposed, according to which strained systems have a higher tendency to undergo Bergman cyclisation.[29] The limitations of the assumptions proposed by Magnus and Snyder were soon clear and attempts were made to produce more precise data. Nevertheless there is only one example of a classic *ab-initio* calculation (STO-3G, HF level) for the transition state on enediynes; the results were inconsistent, leading to geometries where the multiple bonds were too short.[30] More complex systems were never computed using this approach.

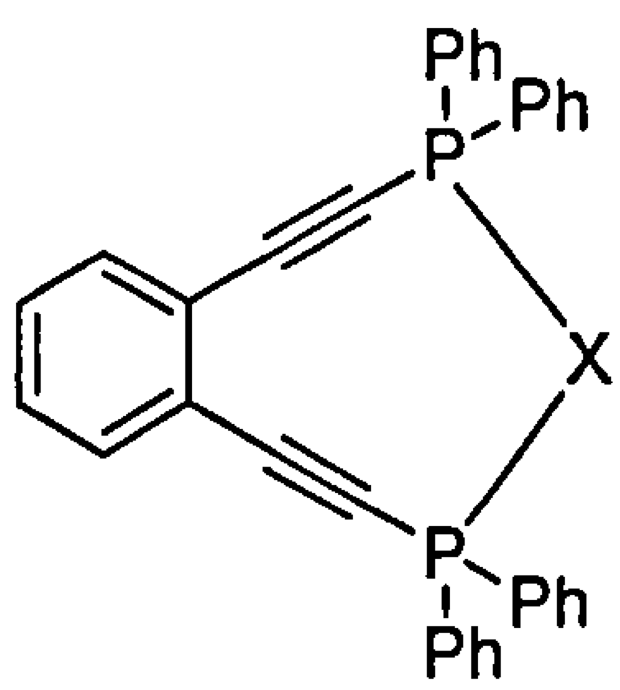
More recently developments in computational chemistry have permitted a better theoretical and mathematical treatment of the problem. There is now a monumental amount of literature on the subject and several *ab-initio* or DFT methods are being modified to better handle the complexity of the calculations.[4] Handling of the multiplicity of the biradical seems to be the major trouble. In spite of the improvements achieved, to date there is no method to reliably calculate the difference in energy between the ground state and the transition state. On the other hand, the importance of Nicolaou's *cd* distance has never been ruled out. In a recent paper Schreiner stated that there is clearly no predictive linear relationship between *cd* and cyclisation activation enthalpy; yet it underlined the validity of the critical range where cyclisation should occur spontaneously, expanding it to 2.9-3.4 Å.[31] He also found that a pure DFT method gives better results than CASPT2 and CCSD(T) or a hybrid method such as B3LYP. Moreover, there is no precedent of either spontaneous cyclisation for large *cd* distances (> 3.7 Å) nor of stable enediynes with *cd* < 3.1 Å.[32] It is now accepted that *cd* is not the sole contributor to the activation energy for enediyne cyclisation, yet it influences and coarsely correlates with the temperature at which enediynes cyclize for systems without significant molecular strain contribution to the activation barrier.

3.1.4. New Approaches in Triggering the Bergman Cyclisation: Complexation.

There are some fundamental characteristics for the (*Z*)-enediyne systems in order to be of practical therapeutic application: to achieve an effective delivery, to be stable under physiological conditions (notably pH and temperature) and to possess a removable blocking system to trigger the cyclisation.

The literature on enediynes continues to grow rapidly and a comprehensive treatment of all aspects of their chemistry is beyond the point of this introduction. Exhaustive information has been reported in a series of very good reviews.[8,26,33] Here we rather focus our attention on the one aspect that concerns our contribution to the subject: distinct methods of triggering the Bergman cycloaromatization. Chemists have extensively focused on this feature. For instance, a mimic of the natural occurring enediyne calicheamicin has been synthesised, in which the original trisulfide was substituted by a thioacetyl group activated by nucleophilic oxygen; the mimic showed higher DNA-damaging activity than its natural counterpart.[11]

Among the factors that trigger the Bergman cyclisation, the *cd* distance and the strain energy of the ground state of the reacting molecule play a key role (*vide supra*). Synthetic chemists have mainly utilised strained ring systems to get the acetylenic *termini* close to one another.[13,34] However, alternative strategies have been reported: one is the design of an acyclic enediyne with heteroatoms capable of chelating a metal. The first successful example of this strategy is molecule **26** (Figure 3.3).[35]

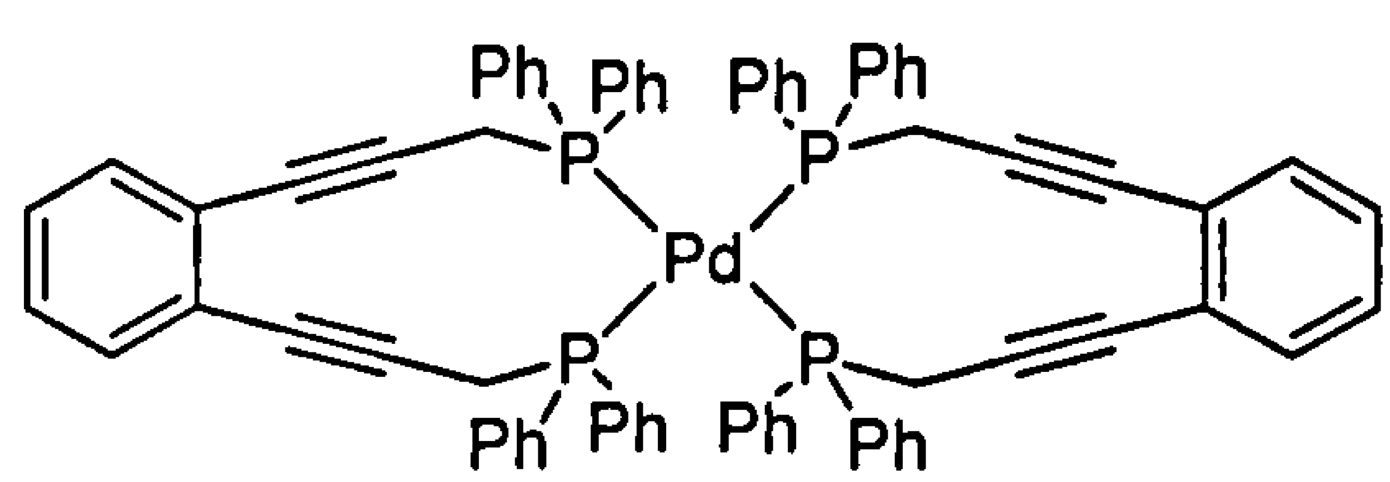


X= no metal, *cd*= 4.1 Å
X= $PdCl_2$, *cd*= 3.3 Å
X= $PtCl_2$, *cd*= 3.3 Å
X= $HgCl_2$, *cd*= 3.4 Å

26

Figure 3.3

Phosphine **26** is stable under an inert atmosphere, able to bind to nucleic acid fragments and relatively easy to synthesise. On the other hand, when complexed to a suitable metal (such as biologically-compatible *cis*-platin and palladium), **26** underwent a very rapid cyclisation to the corresponding naphthalene. Noteworty is the fact that in spite of shortening of the *cd* distance upon addition of $HgCl_2$, the mercury complex did not cyclize upon heating. Later, other authors demonstrated the importance of the oxidation state of the chelating metal.[36]
In particular, Zaleski prepared bis(1,2-bis(diphenylphosphinoethynyl)benzene)palladium (0) **27** (Figure 3.4).[37]

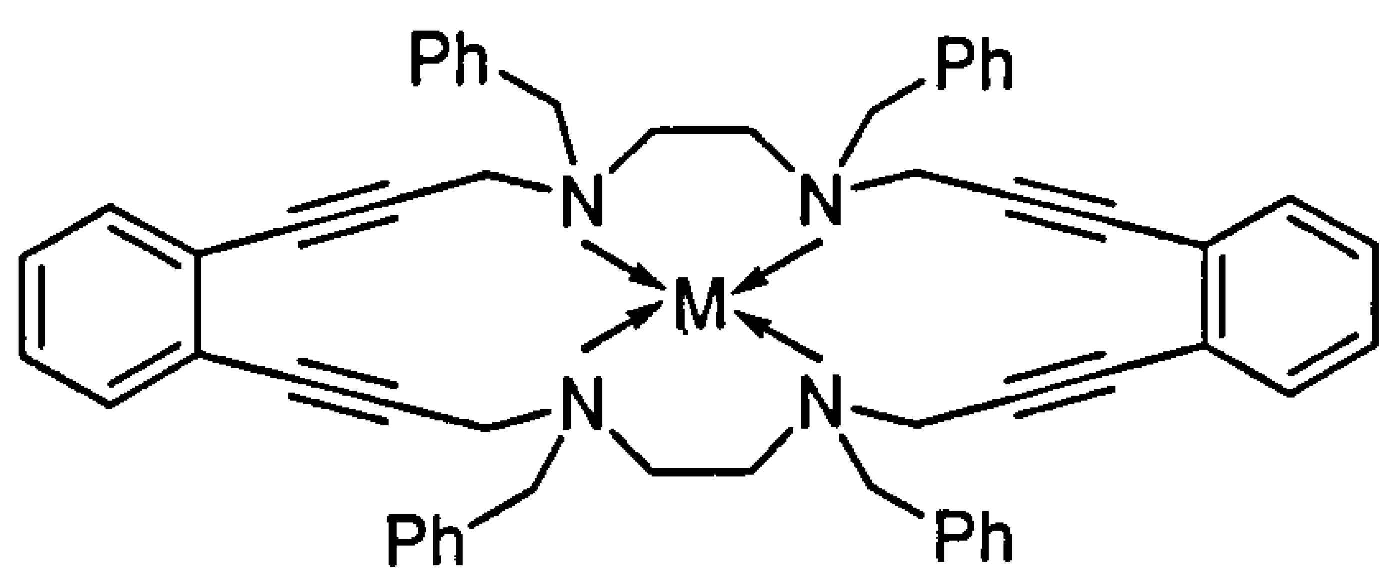


27

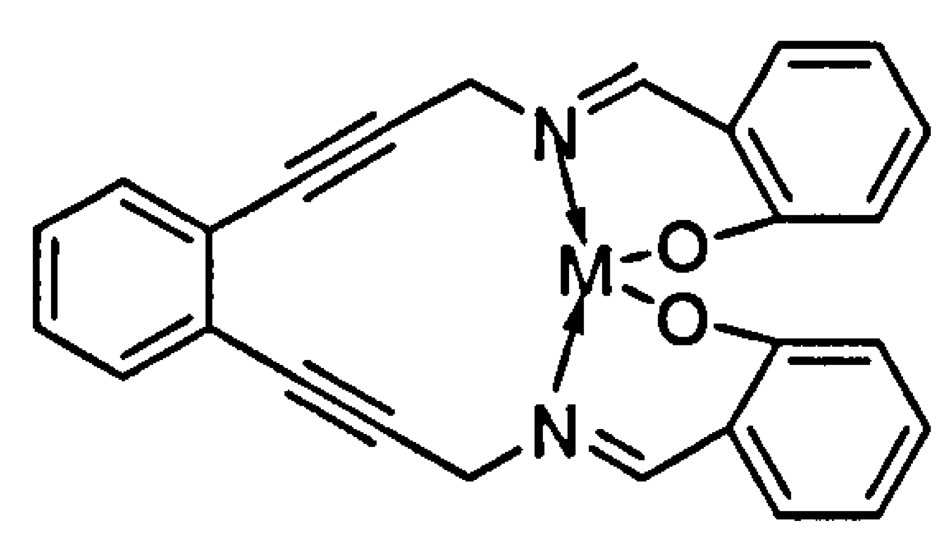
Figure 3.4

Although strikingly similar to **26**, **27** was recalcitrant to thermal cyclisation. This, the authors reported, was partially due to the relatively large *cd* distance (3.47 Å) imposed by the tetrahedral geometry of the Pd (0) centre. More importantly, they suggest that the square-planar ground-state geometry of the Pd(II) centre in **26** served to more closely approach the required planar transition state geometry of the Bergman cyclisation. In their case, the ligand field stabilized tetrahedral geometry of the metal centre rendered complex **27** remarkably stable.

In spite of being a generally reliable method of inducing strain in the molecule,[38] complexation gave some contradictory results. Nitrogen containing cyclic enediynes **28** also experienced lowering of the cyclisation temperature upon complexation with metals (Cu^{2+}, Ni^{2+}),[39] whereas acyclic ones **29** cyclized at higher temperature under the same conditions (Figure 3.5).[40]



28



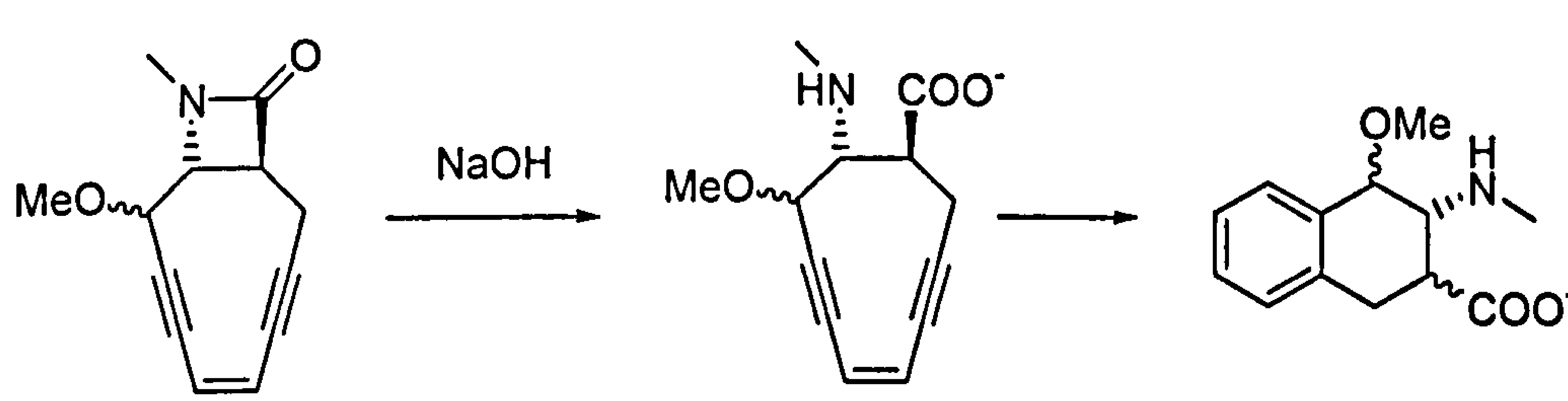
29

Figure 3.5

A different approach has been to incorporate crown ether rings in the enediyne system. Complexation by cations (such as Na^+ or K^+) couples the molecular recognition by the crown to the induction of strain in the enediyne moiety sufficient to facilitate the cyclisation.[41]

3.1.5. New Approaches in Triggering the Bergman Cyclisation: Chemical Methods.

Guanti fully exploited the concept that it is the difference in strain energy between the starting material and the product that governs the ease of cyclisation.[42] He prepared a diastereoisomeric mixture of compound **30**, which he christened lactendiyne (Scheme 3.8).

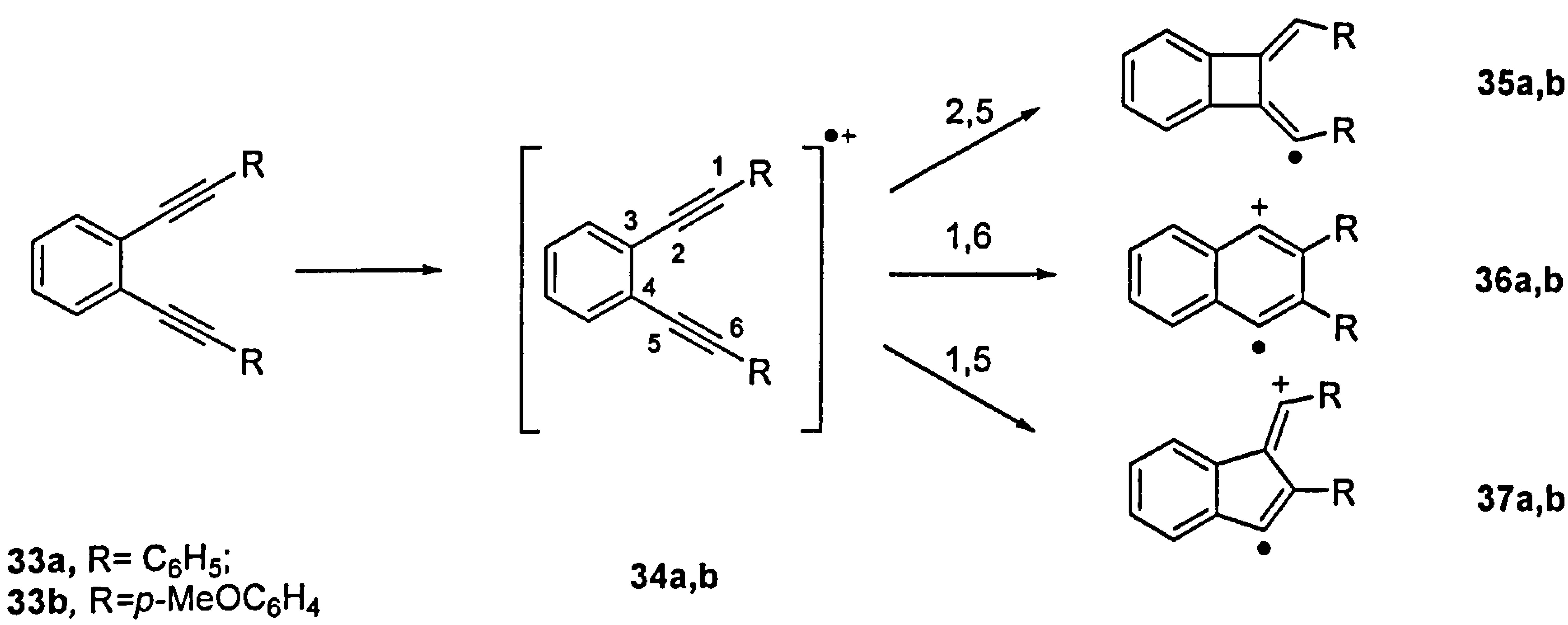


30 **31** **32**

Scheme 3.8

Heating **30** for several hours in the presence of 1,4-cyclohexadiene gave no reaction. Very simple MM calculation showed that the heat of formation of the product of the Bergman cyclisation for **30** is extremely high. Scarce reactivity of a ten-membered enediyne *trans*-fused to a dioxolanone had also been reported by other authors.[43] On the other hand, upon treatment of **30** with 1M NaOH in the presence of 1,4-CHD, the reaction afforded diastereoisomers **32** quantitatively. Again, calculation foresaw that in spite of lowering the strain by going from **30** to **31**, the lowering of the corresponding transition states is much more enhanced.

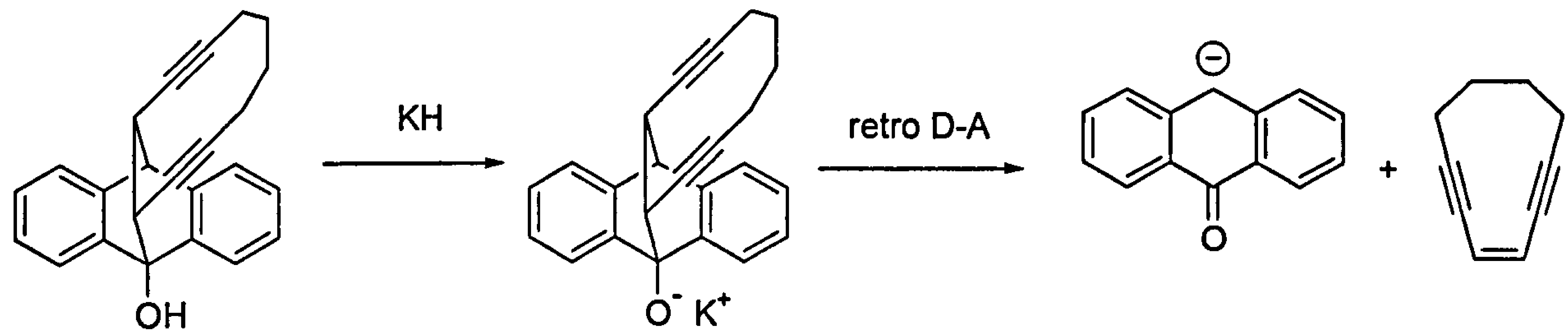
Oxidation of aryl enediyne derivatives to the corresponding radical cations has also proved very efficient in triggering cyclisation (Scheme 3.9).[44]



Scheme 3.9

The oxidation from **33a** and **33b** to **34a** and **34b** could be achieved chemically, photochemically and electrochemically. In all cases the only observed products were derived from intermediates **37a** and **37b**, thus showing a preference for the 1,5-cyclisation mode for the radical cations, unlike their neutral counterparts.

Alkoxide acceleration of a retro Diels-Alder reaction is one of the most elegant triggering systems in the aromatisation of cyclic enediynes that has been reported.[45] In a landmark paper Evans reported that the rate of the oxy-Cope [3,3] sigmatropic rearrangement is dramatically increased upon conversion of the alcohol to the potassium alkoxide.[46] The same concept was applied to lower the activation energies of the retro Diels-Alder reaction, which normally requires quite harsh thermal conditions.[47] Recently, Nicolaou designed and synthesised compound **38**, which was stable under neutral or acidic conditions (Scheme 3.10).



38 39 40 41

Scheme 3.10

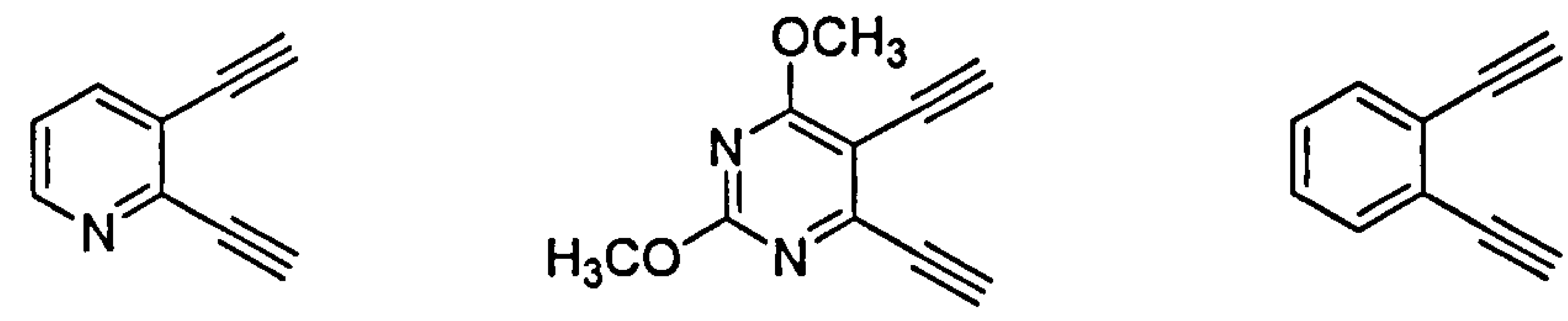
However, deprotonation to form the alkoxide **39** immediately initiated the desired cycloreversion. The resulting cycloenediyne **41** underwent Bergman cycloaromatisation at room temperature ($t_{½}$ = 18 h at 37 °C).

Electronic contribution to the stabilisation of either the ground state or the transition state of enediynes has also been studied. Schmittel and Kiau demonstrated that electron-withdrawing groups attached to the triple bond termini modestly lowered the activation enthalpy of cycloaromatisation. It was suggested that this was the result of decreased steric repulsion between the cyclising in-plane π orbitals.[48] Moreover, Maier and Greiner hypothesized that an electron-donating arene attached to the double bond inhibited cyclisation by stabilizing the ground state of the starting material more than destabilizing the transition state.[49] In a series of quinone/dihydroquinone enediynes pairs the quinone was found to react significantly faster than the dihydroquinone analogue.[21,50] For instance, quinone **42** has a half-life of 2.6 hours at 110 °C, whereas the parent dihydroquinone **43** has a half-life of 74 hours at the same temperature (Figure 3.6).

42 43

Figure 3.6

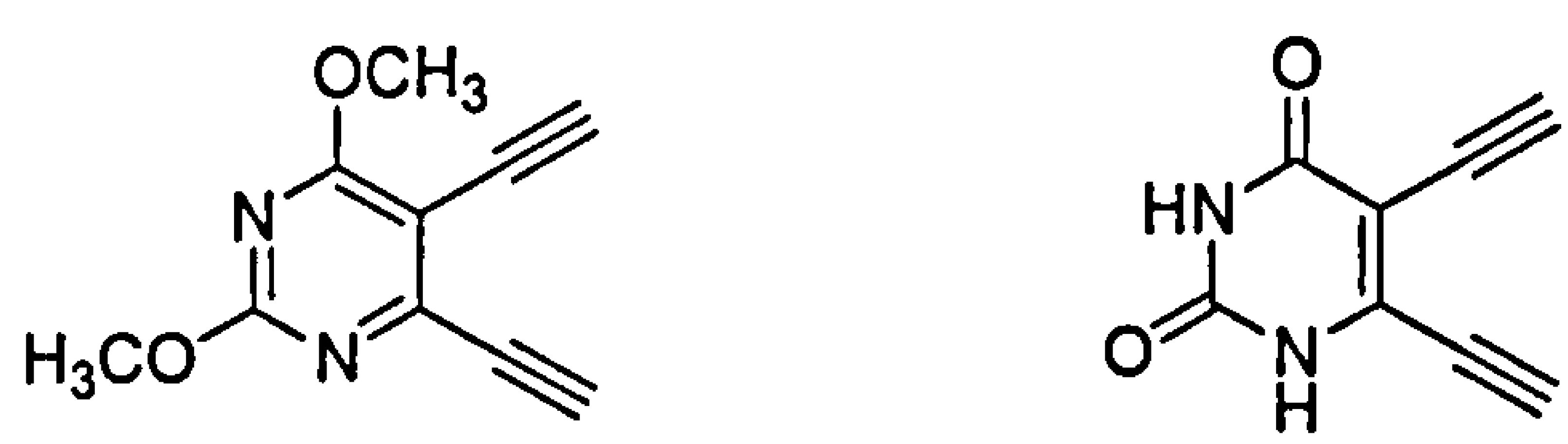
These hypotheses were confirmed when electron-deficient heteroarenediynes **44** and **45** showed higher reactivity compared to 1,2-diethynyl benzene **46** (Figure 3.7).[51]



44 45 46

Figure 3.7

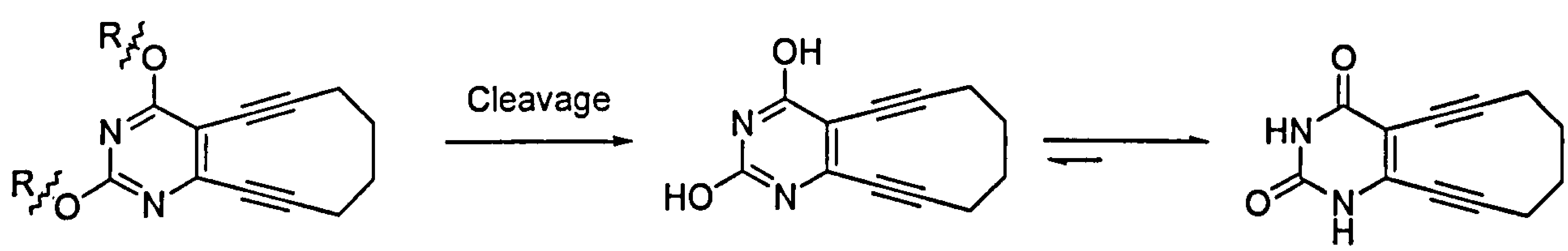
This concept has in fact been hinted as a possible mean to trigger Bergman cyclisation. It was hypothesized that the lactam and lactim tautomeric forms can be considered analogous to the electron-deficient quinone and aromatic dihydroquinone, respectively. Molecules **47** and **48** have been synthesized and tested thermally (Figure 3.8).[52] As expected, the rate of cyclisation was enhanced 25-fold on going from **47** to **48**.



47 48

Figure 3.8

These results render plausible a rationale where a stable lactim could undergo cyclisation upon tautomerization into its lactam form (Scheme 3.11). Work in this direction is currently in progress in Russell's group.

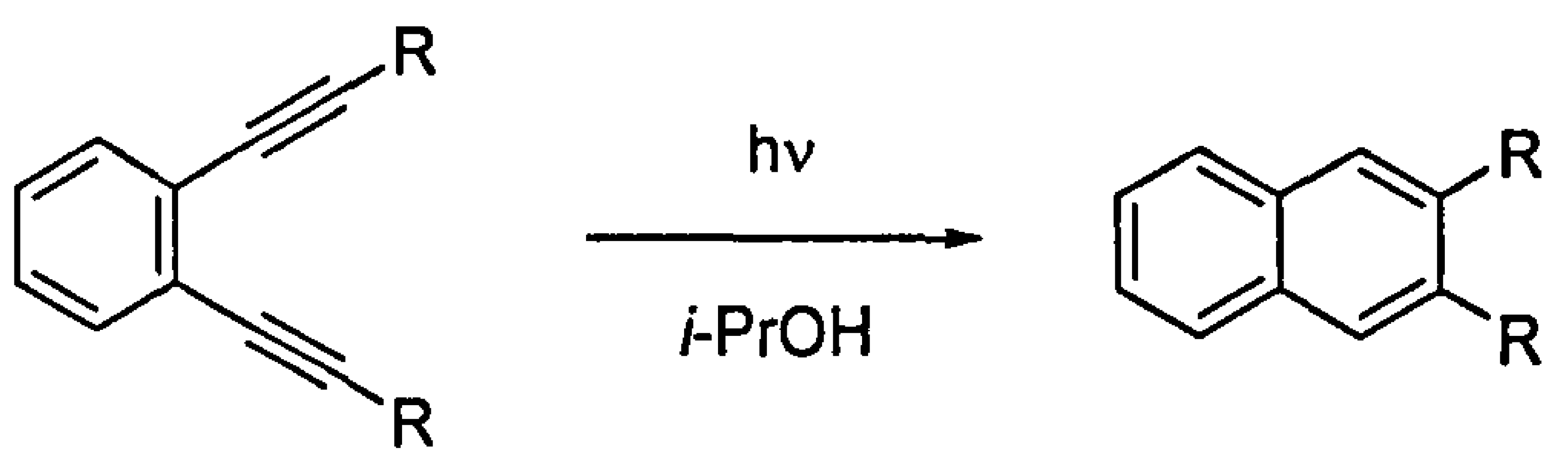


32 33 34

Scheme 3.11

3.1.6. New Approaches in Triggering the Bergman Cyclisation: Photochemistry.

Finally, a brief account of the photochemical methods employed to activate cyclisation is presented. Basak's work on photochemical oxidations has been already mentioned.[44] Strictly speaking, however, this reaction does not fall in to the Bergman cyclisation category, being a 1,5 biradical recombination rather than a 1,6. Evenzahav, Turro and Nicolaou were the first authors to report a purely photochemically activated Bergman cycloaromatization (Scheme 3.12).[53]



49 **50**

Scheme 3.12

Funk then prepared a series of aromatic enediynes which all underwent cyclisation upon irradiation (Figure 3.9).[54]

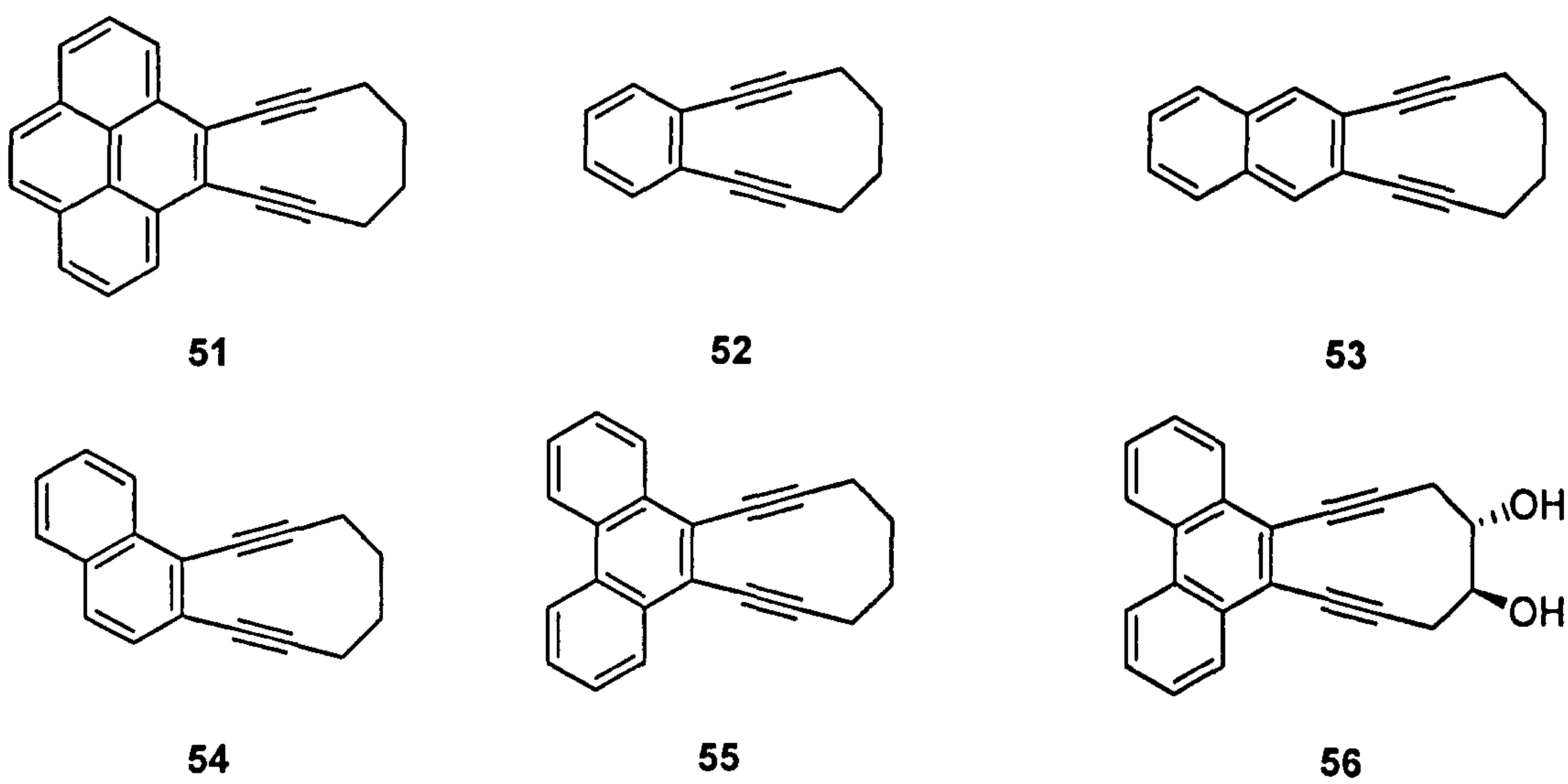


Figure 3.9

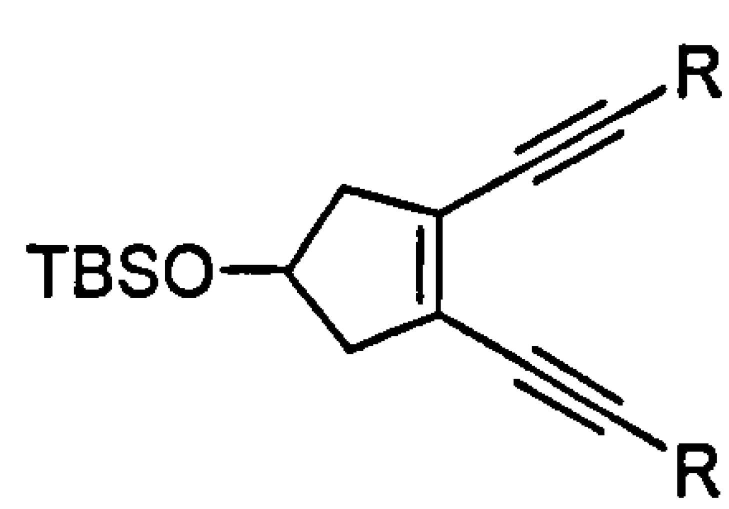
Compound **51** also reacted when exposed to sunlight. Cyclisation proceeded very slowly if not at all in the presence of less then 10 equivalents of 1,4-CHD, a result that spoke for a reversible process. Moreover, water-soluble analogues of the enediyne **56** were found to be effective in binding and cleaving single DNA strands upon irradiation. In a follow-up to their communication, Turro and Evenzahav published a very exhaustive study on the mechanism of photoaromatization of enediynes **57** and **58**. They based their conclusions on experimental data and on studies on similar systems that have been extensively covered in the literature (Figure 3.10).[55]

57 58

Figure 3.10

Results are consistent solely with a radical process. The enediynes are first excited to their singlet states (probably of the acetylenic unit); a Bergman-type cyclisation then takes place to forms a discrete 1,4-naphthyl biradical intermediate, capable of abstracting two hydrogens from an isopropyl molecule. A single-step concerted mechanism to form the biradical is ruled out, and so are purely ionic or radical cation intermediates. Side products are consistent with an intersystem crossing to the triplet state, the likeliness of which to occur is related to the geometric conformation of the enediyne.

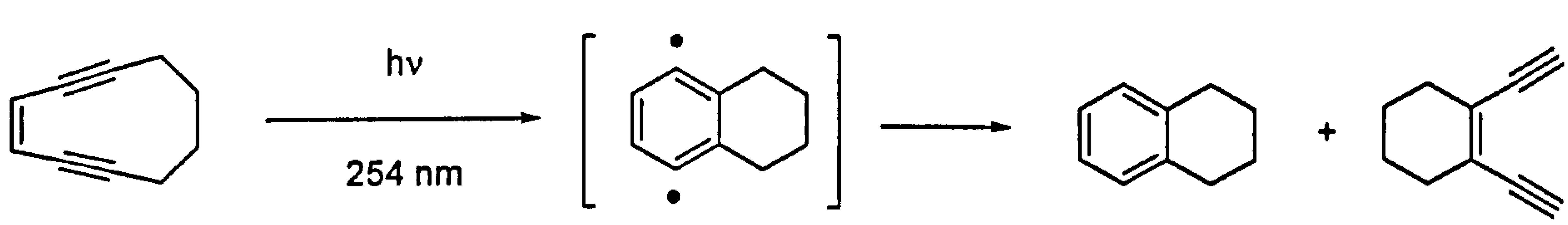
The first example of photochemical cyclisation of aliphatic enediynes has been recently reported by Hirama.[56] Compounds of the type **59** were irradiated in a variety of solvents, showing remarkably diverse reactivity depending on the nature of the R group (low yield – 3%- for R=H; no reaction for R=TMS or Ph; good yield – 71%- for R=Me) (Figure 3.11).



59

Figure 3.11

Studies conducted in deuterated solvents once more supported the intermediacy of 1,4-phenyl biradicals. Interestingly, photochemical studies conducted by the same group on the strained ten-membered enediyne **60**, gave a mixture of two compounds **62** and **63** (Scheme 3.13).

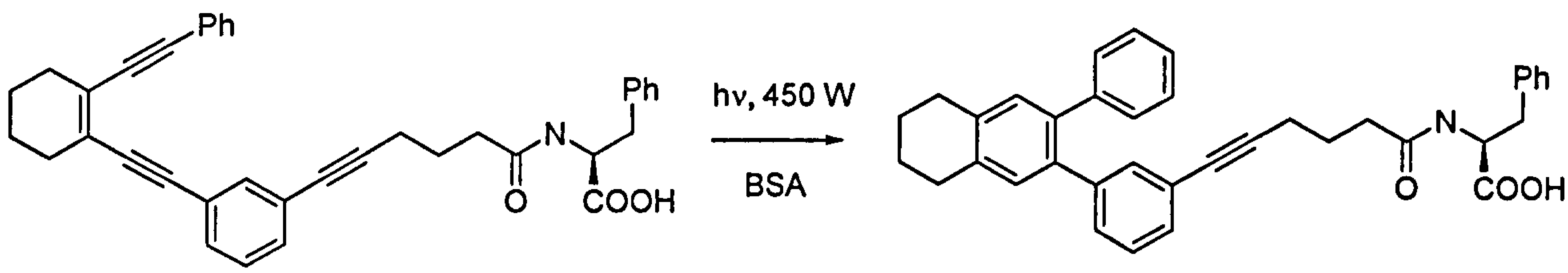


60 61 62 63

Scheme 3.13

Formation of **63** is remarkable because this enediyne should arise from the retro-Bergman reaction of the hypothetical diradical intermediate **61**, and because **63** has never been isolated in the thermal reaction of **60**.

Finally, a new alicyclic enediyne has been recently designed and synthesized by Jones. Upon irradiation of **64** in the presence of bovine serum albumin (BSA), cylisation product **65** along with degradation of the protein has been recorded (Scheme 3.14).[57]



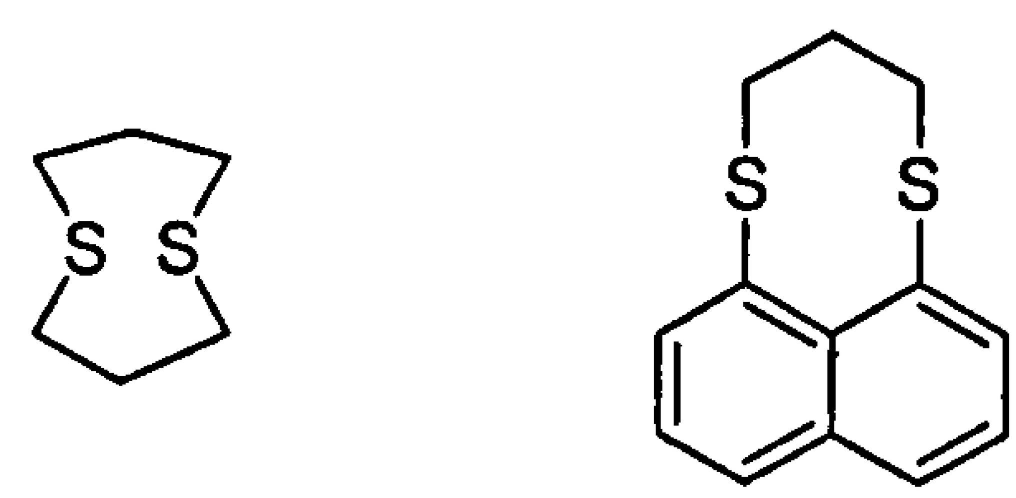
64 **65**

Scheme 3.14

AIMS AND OBJECTIVES

3.2.1. Exploitation of S-S "Through Space" Interactions: Overview and Aims.

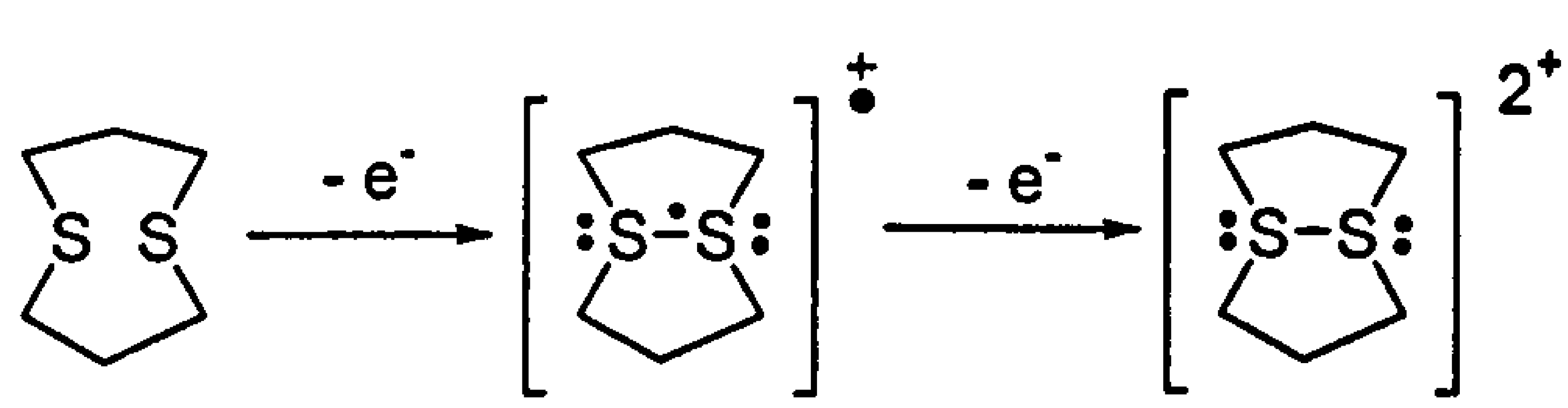
The aim of this work is to develop novel triggering systems for Bergman cyclisation based on exploiting a "through space" interaction between sulfur atoms. It has been reported that chalcogen atoms appropriately arranged in space tend to repulse each other. Typical examples of this interaction are shown by the molecules in Figure 3.12.



66 67

Figure 3.12

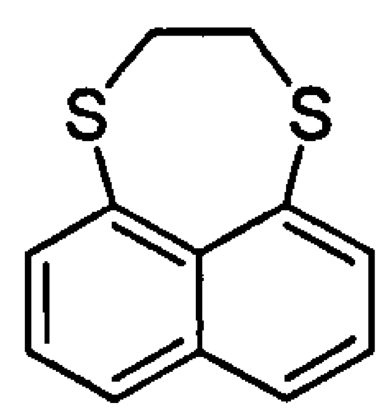
1,5-Dithiacyclooctane **66** has been extensively studied by Furukawa and co-workers.[58] Its instability has been ascribed to the transannular lone pair-lone pair repulsion. Conformation analysis on naphtho[1,8-b,c]-1,5-dithiocin **67** has been already discussed in Section 1.2. Accordingly, these molecules are easily oxidised; upon removal of one or two electrons from the chalcogen atom,[59] an attractive force operates between the two sulfur atoms, to create a new chemical bond, and a "dication" (Scheme 3.15).[60]



66 68 69

Scheme 3.15

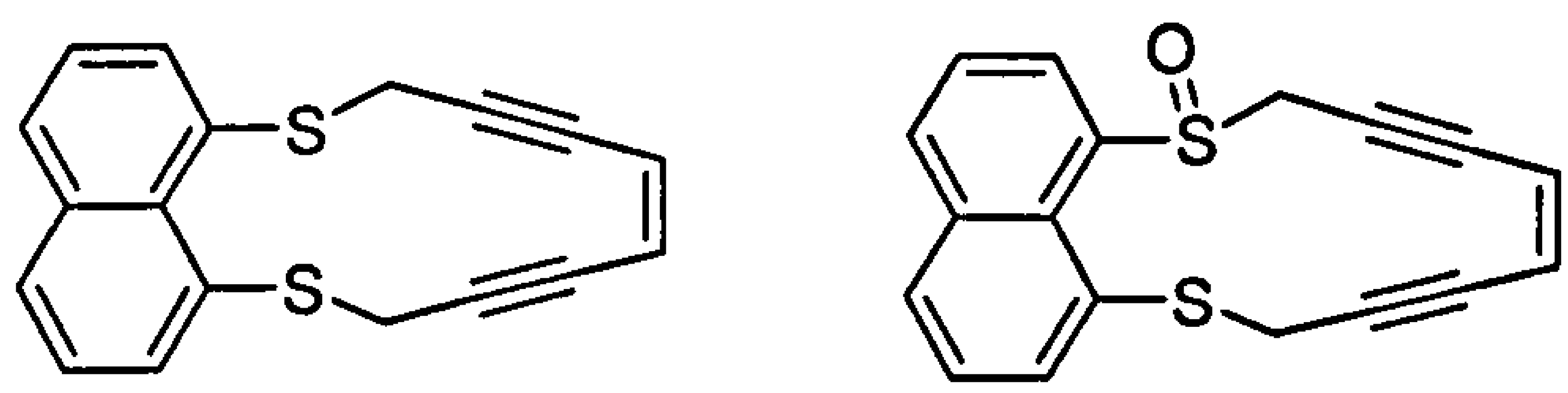
Cyclic voltammetry of **66** and related compounds shows an extremely low E_p, which implies dications stable enough to be detected.[61] Overall the formation of the dication brings the two sulfur atoms closer together. Furukawa has calculated a shortening of 0.5 Å in the distance between the two sulfur atoms in **55** upon formation of the S-S bond (Figure 3.13).[62]



70

Figure 3.13

The initial aim of this project was to investigate the synthesis of the novel enediynes **71** and **72** (Figure 3.14).



71 72

Figure 3.14

Enediynes **71** and **72** have been designed with a number of key features in mind. Firstly, they should be isolable and stable at room temperature because of their relatively large ring size. However the close proximity of the two sulfur atoms represents a potential triggering mechanism for Bergman cyclisation; formation of a S-S bond should decrease the *cd* distance and/or increase level of strain, thus favouring cyclisation. Possible means of activation are outlined below.

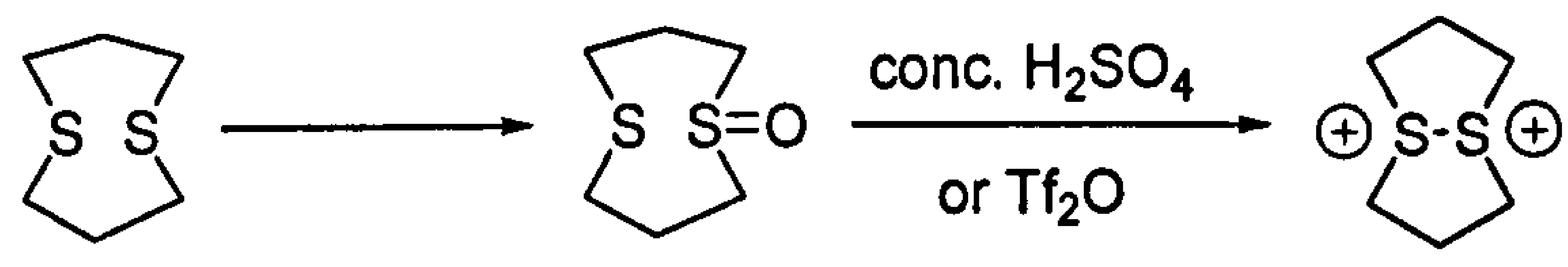
3.2.2. Exploitation of S-S "Through Space" Interactions: Dication-mediated Bergman Cycloaromatisation.

Formation of S-S dication can be achieved by numerous methods. The most reported so far has been by direct chemical oxidation (Ti(III)-H_2O_2;[63] $NOBF_4$ or $NOPF_6$[64]). The tendency of **71** and **72** to form dications can be predicted from their oxidation potential (E_p), measurable through cyclic voltammetry.[65] The lower the value, the easier the oxidation occurs, and the more stable the dication.[66]

Along with chemical methods, physical ones can be evaluated to generate the dication: anodic oxidation[67] and pulse radiolysis[68] -driven oxidations have been reported.

Mono-sulfoxide **72** is of particular interest; derived form the oxidation of **71**, it should be characterised by a stronger attractive force between the two sulfur atoms compared to that of

71, possibly due to the ionic interaction between the partial positive charge on the sulfoxide and the sulfide lone pairs.[69] As a support to this hypothesis, a precedent[70] shows that in compound **73** the S-S distance is shorter than in **66**. The sulfur atoms exist as a quasi-sulfurane so that by treatment of **73** with concentrated H_2SO_4 or Tf_2O the dithia dication **69** was obtained (Scheme 3.16).[64]

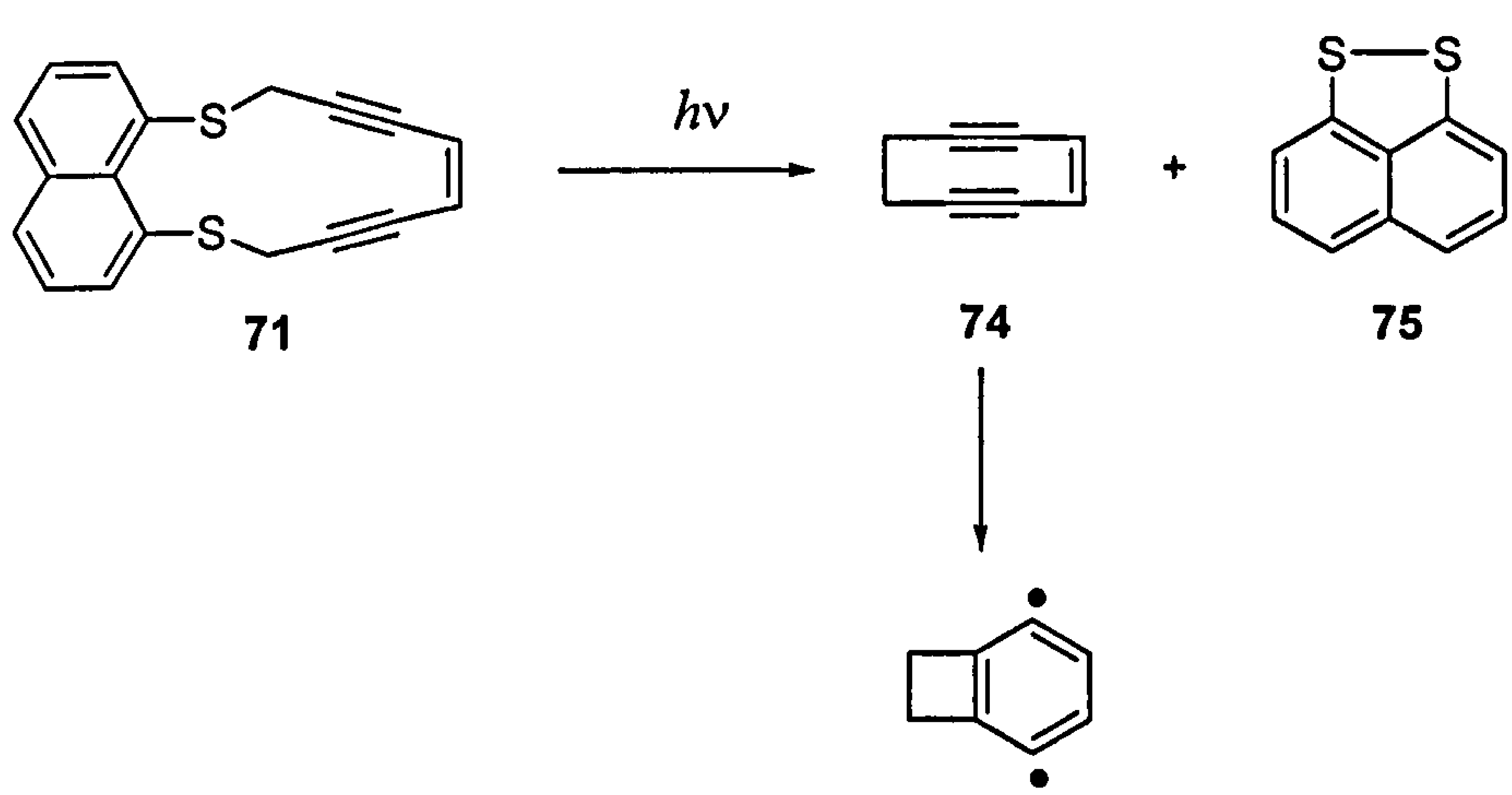


66 73 69

Scheme 3.16

3.2.3. Exploitation of S-S "Through Space" Interactions: Photochemically Induced Bergman Cycloaromatisation.

The transannular interactions between chalcogen atoms, appropriately arranged on a naphthalene skeleton, has been exploited for the photochemical elimination of certain species.[71] Example of this type of chemistry have been presented in Section 1.2. Based on such precedent, a further aim of this project is to explore the possible photochemically induced cyclisation of **71** (Scheme 3.17).



71 74 75

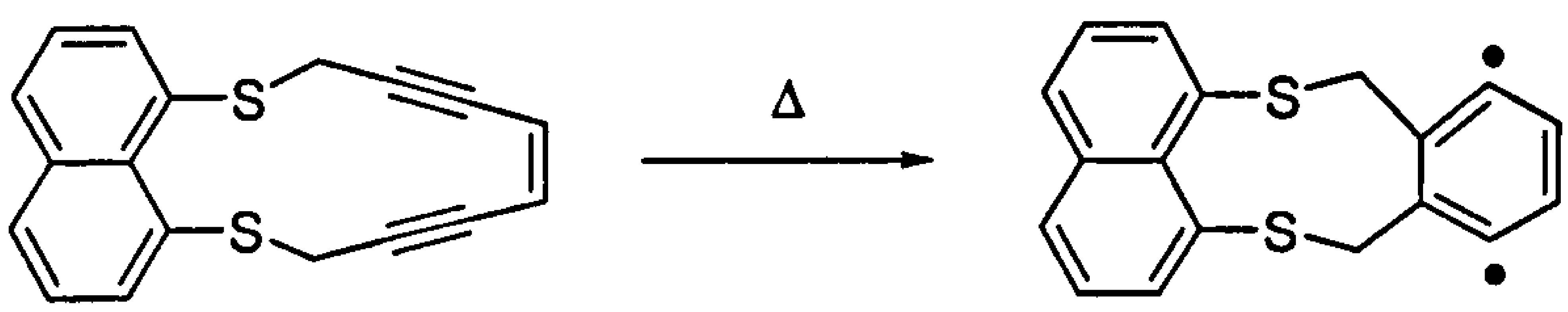
76

Scheme 3.17

It is proposed that the highly unstable enediyne **74** will form first; then, because of the high conformational strain of such a small ring it should rearrange (Bergman cycloaromatisation), to afford the target biradical **76**. Trapping of **76** with a proton source would allow for characterisation of the products. As far as **72** is concerned, we would like to implement the same strategy described in Scheme 3.16. Accordingly, treatment of **72** with conc. H_2SO_4 should promote sulfur-sulfur bond formation.

3.2.4. Thermally Induced Bergman Cycloaromatisation.

Finally, thermally activated **71** should directly give biradical **77** (Scheme 3.18). Similarly compound **72** should also undergo Bergman cycloaromatisation upon thermolysis.



71 **77**

Scheme 3.18

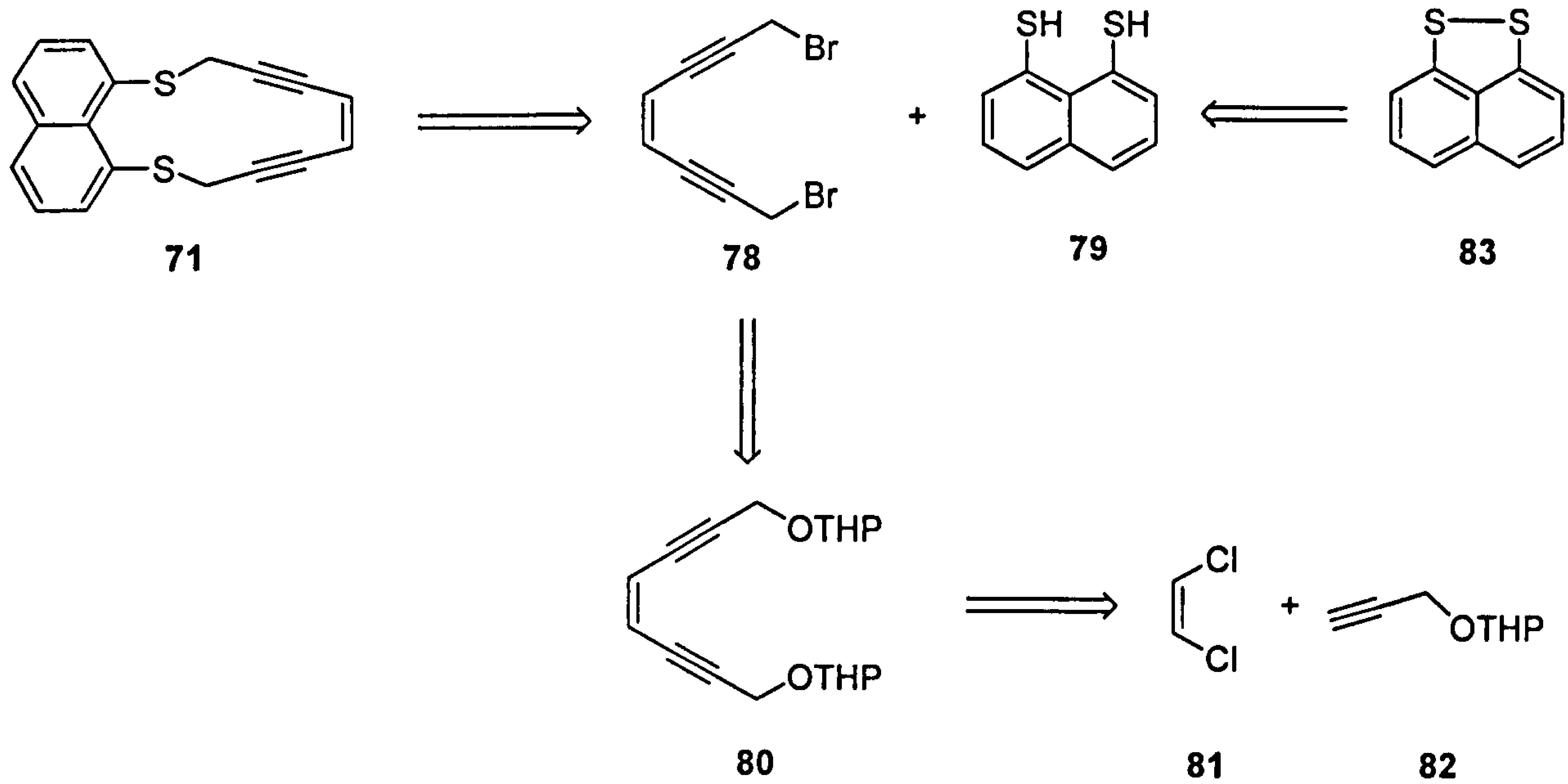
Differential scanning calorimetry[41a] can be used to determine the temperature at which cyclisation occurs. A half life for the cyclisations could also be determined.[50b]

In conclusion, a number of different methodologies can potentially be applied to achieve the desired cyclisation of enediynes **71** and **72**. From a more theoretical point of view, the effect of reducing the *c-d* distance and greatly modifying the strain of the molecule in going from **71** to **72** can be evaluated by comparing the relative cyclisation temperatures. If the strategy we designed for the synthesis of **71** should prove effective (*vide infra*) a whole series of sulfur-containing cyclic enediynes could be prepared. On top of being a novel class of enediynes, a useful comparison between structure and reactivity could hopefully be derived.

RESULTS AND DISCUSSION

3.3.1. Retrosynthetic Analysis.

The retrosynthetic analysis of **71** is quite straightforward (Scheme 3.19).

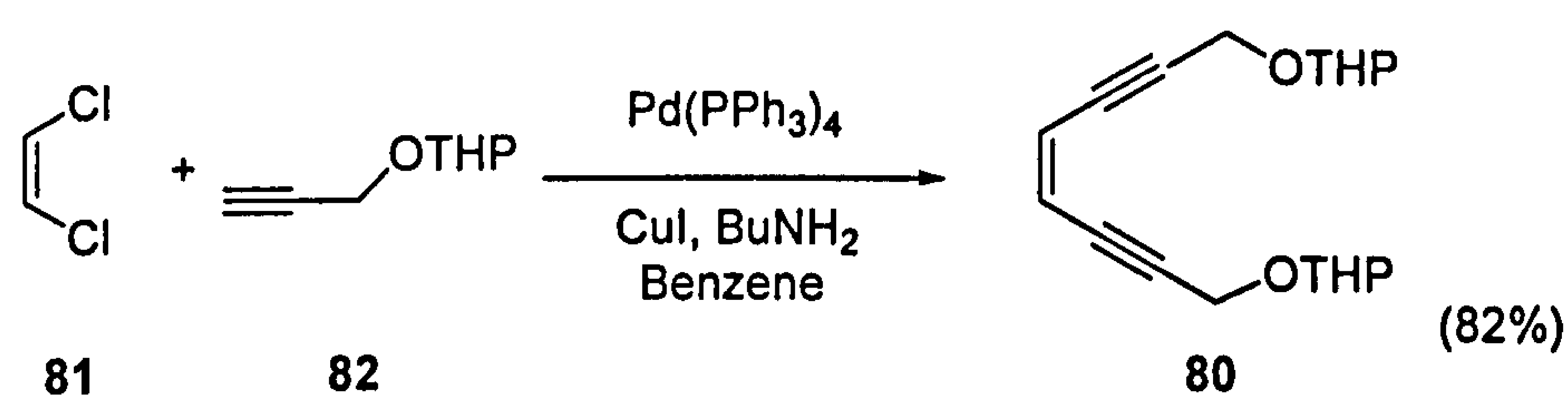


Scheme 3.19

Alkylation of dithiol **79** with the known dibromo enediyne **78** should furnish **71** directly.

3.3.2. Synthesis of 1,8-Dibromooct-4-ene-2,6-diyne.

The synthesis of **78** has been reported.[72] It exploits first a palladium-mediated (Sonogashira) coupling of haloalkene **81** (commercially available) with acetylene **82**; this is one of the most common methods used to assembly enediynes (Scheme 3.20).[73]



Scheme 3.20

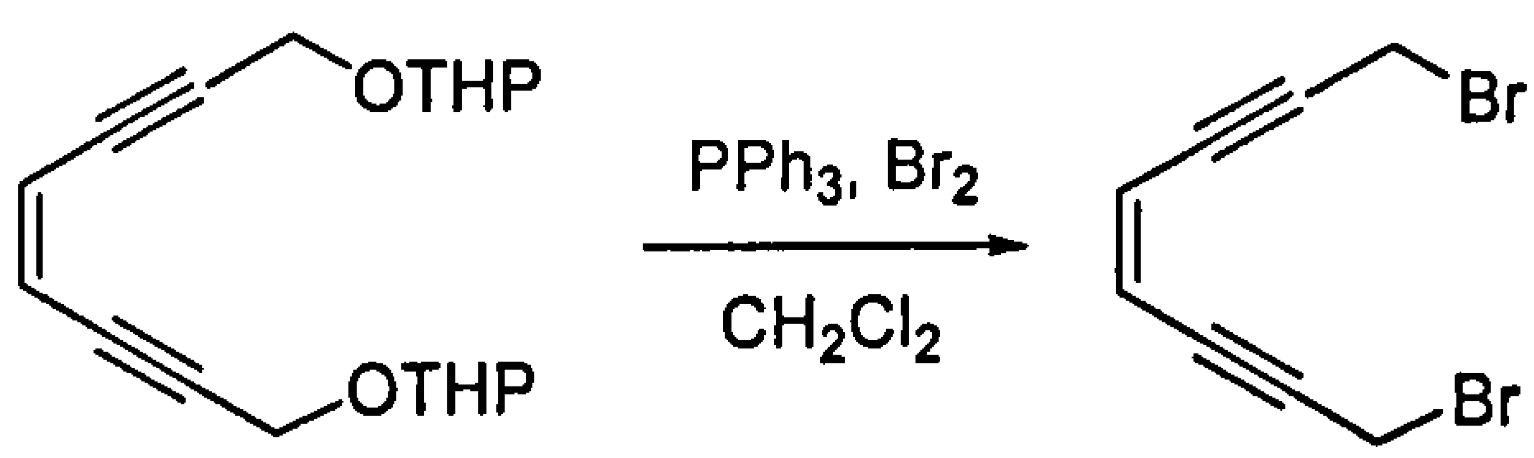
In our hands this reaction proceeded without incident and enediyne **80** was prepared in a comparable yield to that reported in literature (87%). Use of commercially available palladium(0) tetrakis(triphenylphosphine) was not very effective in terms of isolated yields of **80**. Much better results were achieved using catalyst we synthesised ourselves (Scheme 3.21).[74]

$$\underset{\mathbf{84}}{PdCl_2} \quad + \quad \underset{\mathbf{85}}{PPh_3} \quad \xrightarrow[\text{DMSO}]{H_2NNH_2} \quad \underset{\mathbf{86}}{Pd(PPh_3)_4}$$

Scheme 3.21

Palladium(0) tetrakis(triphenylphosphine) **86** was isolated in 100% yield and once stored in the freezer its reactivity remained unchanged for months.

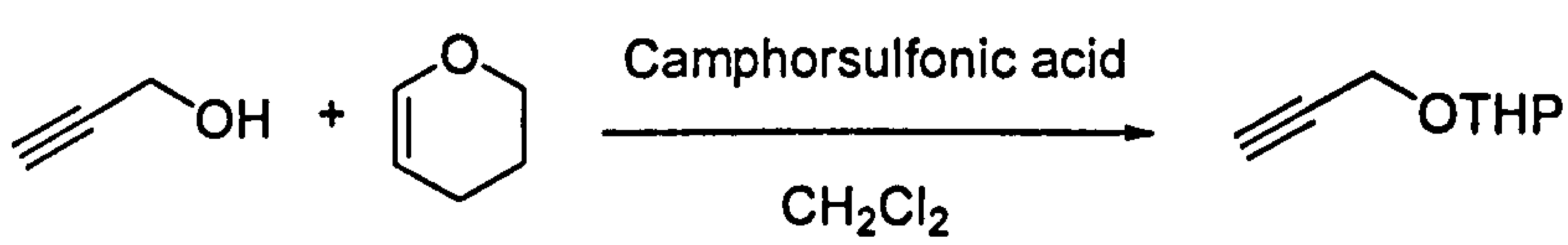
Subsequent treatment of **80** with PPh_3/Br_2 afforded **78** in reasonable yield (Scheme 3.22). Dibromoenediyne **78** was isolated by column chromatography and stored in the freezer, as suggested in the literature.



80 **78** (83%)

Scheme 3.22

The precursor THP-protected ether **82** was prepared as described by Myers (Scheme 3.23).[75]



87 **88** **82** (83%)

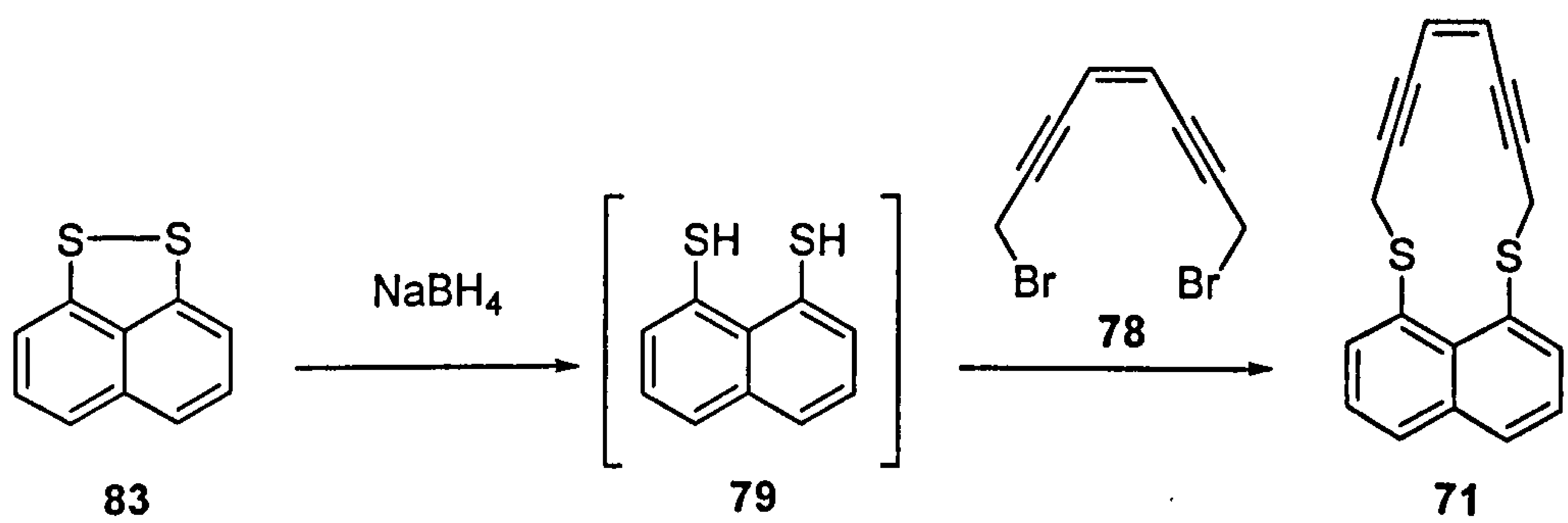
Scheme 3.23

3.3.3. Synthesis of a Novel Macrocyclic *peri*-fused Enediyne.

The preparation of cyclic disulfide **83** was discussed in Chapters I and II. Reduction to the corresponding dithiol **79** was also described. Methodology for the preparation and reduction of **83** adopted here are exactly the same and need no further discussion.

Glass has reported the alkylation of **83** with 1,3-dibromopropane under phase-transfer conditions, using aminoiminosulfinic acid as an *in situ* reducing agent to give a naphthalene-based sulfur-containing macrocycle (see Paragraph 2.2., Scheme 2.29).[76] Analogous alkylation of **83** with enediyne **78**, proceeding along Glass's *modus operandi*, was extensively investigated, without success. Only disulfide **83** was routinely recovered.

A more fruitful approach was inspired by a paper published by Furukawa.[77] Sodium borohydride reduction of **83** in EtOH/THF, followed by addition of dibromide **78** yielded the desired product **71**, although yields were not entirely satisfactory (10-34%) (Scheme 3.24). The reaction has been carried out several times, the yield showing a dependence on the reaction conditions: dilute solutions and slow addition of the alkylating agent seemed to favour the desired product; however reaction times were consequently longer, so as to favour the oxidation of the dithiol **79** back to the disulfide **83**. The best yields were achieved by tuning the dilution and the rate of addition so as to reduce the reaction times within five hours.



Scheme 3.24

Spectroscopic data were consistent with the structure of **71**. Surprisingly, the methylene protons appeared as singlets in the ^{1}H NMR. Enhanced resolution NMR showed these signals to be in fact split into what could be a double doublet. The tiny coupling constant (about 0.4 Hz), however, is more likely assignable to long-distance coupling with the alkene protons rather than to geminal coupling. The presence of a double doublet implies that the alkyl protons are coupling with both the alkene protons. If that held true, the alkene signals should have been a triplet, which was confirmed in the enhanced resolution spectrum. If the splitting of the alkyl signals was due to geminal coupling, the alkene signals would have been a double doublet instead.

We succeeded in growing crystals of compound **71** by slow evaporation of its dichloromethane solution in a hexane atmosphere. Crystallographic data helped determine the conformation of the molecule and the spatial disposition of the protons (Figure 3.15).

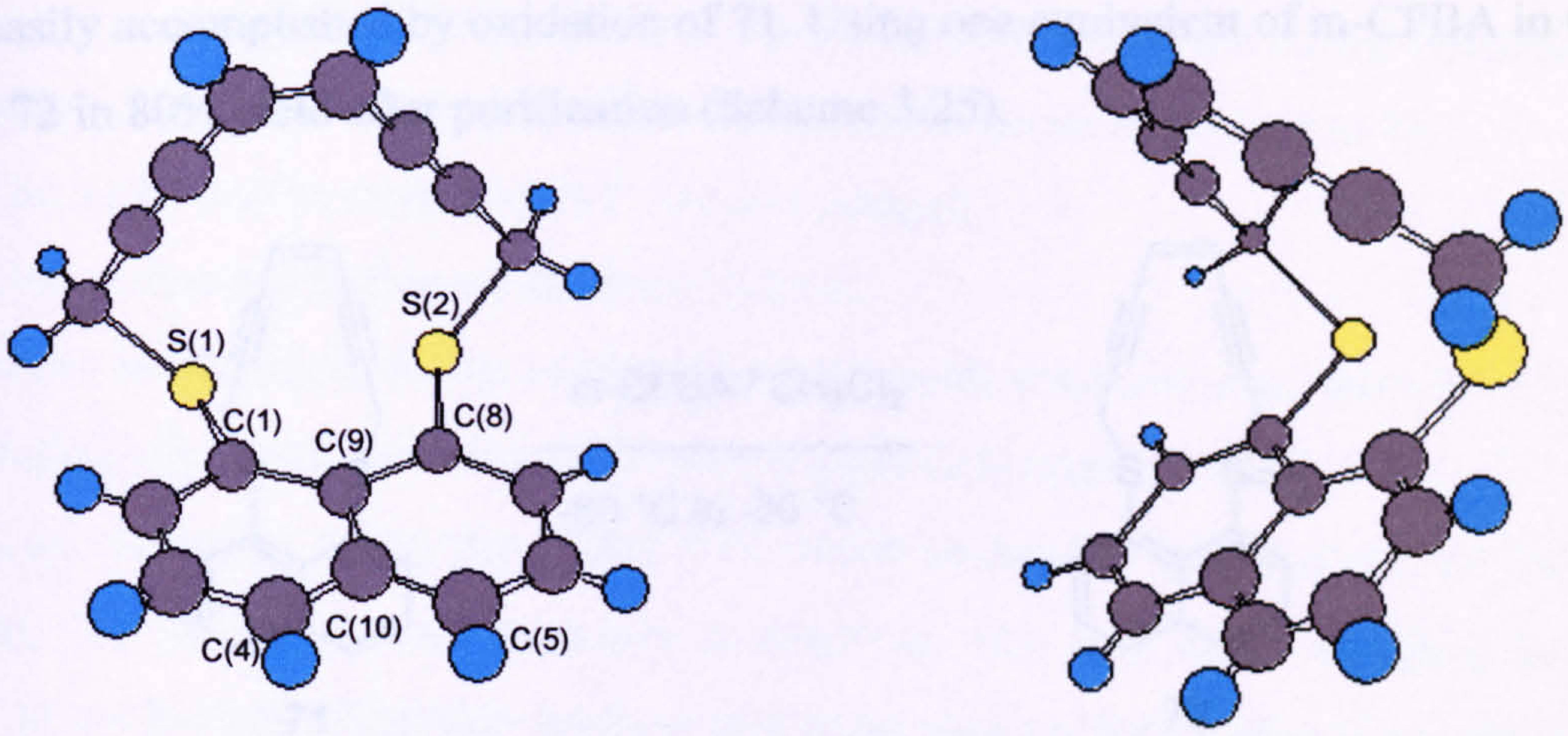
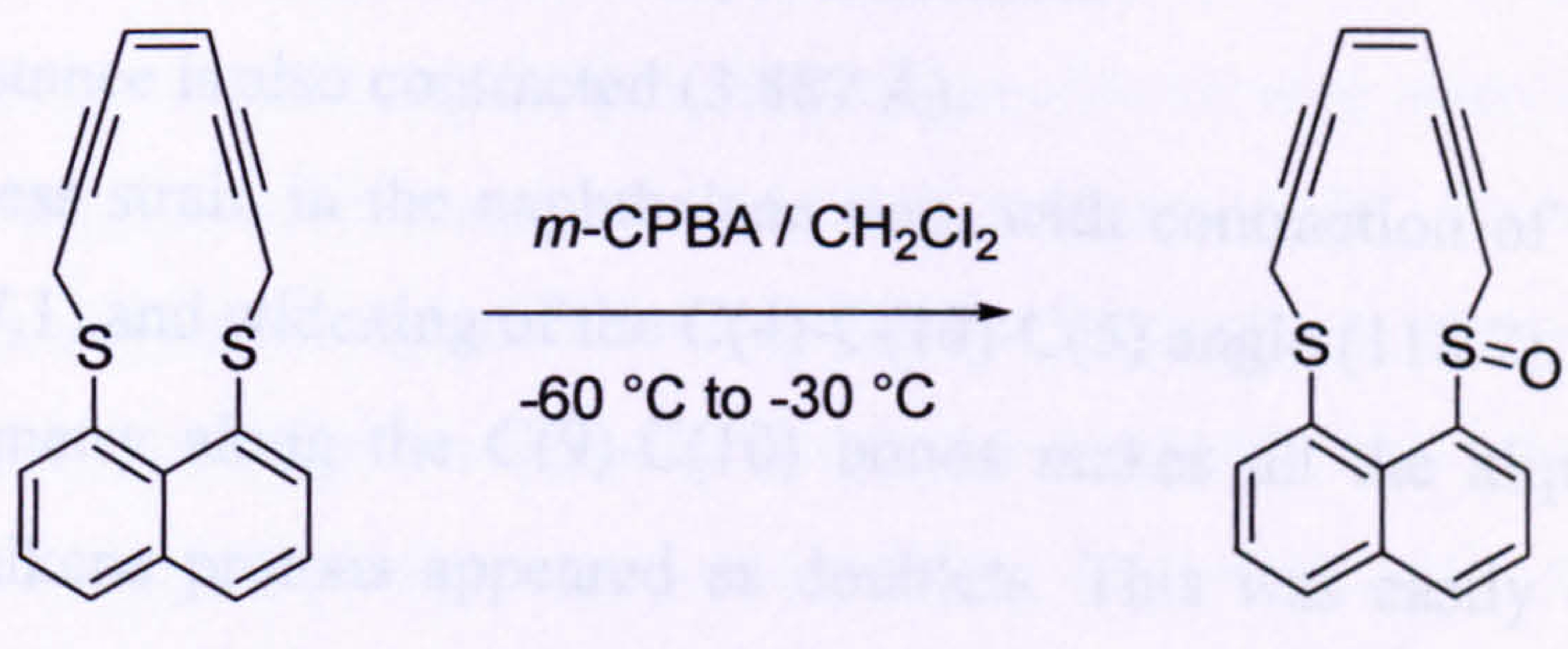


Figure 3.15

The molecule sits in an envelope-type structure. The frontal view on the left hand side shows virtually no strain on the two acetylenic units (CH_2-C≡C angles of 177.5 and 178.2). Relatively pronounced is the widening of the S(1)-C(1)-C(9) and S(2)-C(8)-C(9) angles (122.7 and 125.5, respectively). The molecule is almost symmetrical in respect to a plane passing through C(9)-C(10) and bisecting the double bond. Quantitatively more important is the strain induced on the naphthalene ring: C(1)-C(9)-C(8) angle is expanded to 127.9 degrees, whereas C(4)-C(10)-C(5) is contracted to 118.2. The S-S distance is 3.121 Å, still much shorter than twice the van der Waals radius of sulfur (3.70 Å).[62] The two sulfur atoms lie slightly out of the naphthalene plane, one above and one below. More importantly, the *c*-*d* distance is set at 4.087 Å. Following Nicolaou's prediction, the enediyne did not cylise spontaneously at room temperature.

3.3.4. Oxidation of the Novel *peri*-fused Enediyne. Synthesis of the Sulfoxide.

Oxidation of sulfides to sulfoxides is an extensively reported transformation.[78] Synthesis of **72** was easily accomplished by oxidation of **71**. Using one equivalent of m-CPBA in CH_2Cl_2 afforded **72** in 80% yield after purification (Scheme 3.25).



71 **72**

Scheme 3.25

As for **71**, X-ray analysis of **72** provided a good deal of information (Figure 3.16). Crystals of compound **72** were grown in an identical fashion as those of **71**.

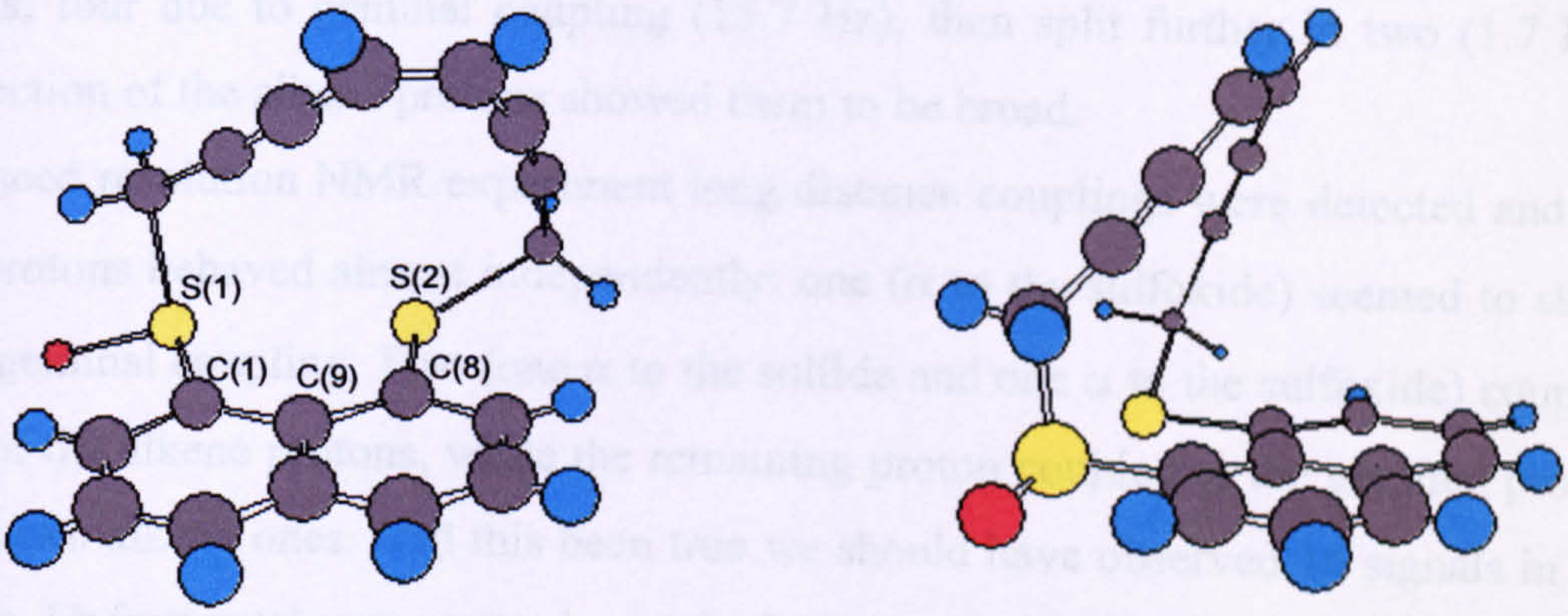


Figure 3.16

The most striking feature is the loss of symmetry along the C(9)-C(10) plane: the aliphatic carbon attached to the sulfide is pointing "out" whereas the one attached to the sulfoxide is pointing "up", almost in line with the sulfur atom and the aromatic carbon C(1). The C(8) – S(2)-CH_2 angle at the sulfide is 102 degrees, a value comparable with standard sulfides.[79] The sulfoxide is by no means symmetric; the CH_2-S(1)-O angle (100.8) is much smaller than the C(1)-S-O bond (106.3). This brings the oxygen almost onto the plane of the naphthalene ring.

We expected an attraction between the lone pair of the sulfide and the partial positive charge on the sulfoxide. As a consequence, there are other differences compared to **71**.

1. The sulfur-sulfur distance (2.977 Å) is shortened.
2. The *cd* distance is also contracted (3.887 Å).
3. There is less strain in the naphthalene ring, with contraction of the C(1)-C(9)-C(8) angle (127.1) and widening of the C(4)-C(10)-C(5) angle (118.7).

The loss of symmetry along the C(9)-C(10) bonds makes all the aliphatic protons non-equivalent. The alkene protons appeared as doublets. This was easily assigned as due to coupling to each other. That also implied that there was no long-distance coupling to the methylene protons. These in turn, had a far too elevated multiplicity. Any of the four should have appeared as doublets (due to the exclusive geminal coupling), giving a total of eight signals, roughly of the same intensity. Instead there was a total of twelve signals. It seemed that one of the two CH_2 units (α to the sulfide) gave the expected four peaks, with coupling constant consistent with a geminal relationship (16.5 Hz). The CH_2 α to the sulfoxide gave eight signals; four due to geminal coupling (15.7 Hz), then split further in two (1.7 Hz). Closer inspection of the alkene protons showed them to be broad.

In the enhanced resolution NMR experiment long distance couplings were detected and the methylene protons behaved almost independently: one (α to the sulfoxide) seemed to show exclusively geminal coupling. Two (one α to the sulfide and one α to the sulfoxide) coupled also to one of the alkene protons, while the remaining proton coupled to the geminal proton and both the two alkene ones. Had this been true we should have observed 16 signals in the alkene region. Unfortunately we counted a total of twenty-six peaks, making it impossible to pin down the origin of the splitting. It seems very likely that overlapping of alkyl proton signals and the minuteness of the coupling constants involved are responsible for this apparent mismatch. The nature and relationship of these couplings is still unclear; although intriguing, an exhaustive spectroscopic study on these molecules was beyond the point of this thesis and we were already satisfied with the fact that the ^{1}H NMR and ^{13}C NMR spectra obtained were consistent with the proposed structure of both **71** and **72**.

3.3.5. Evaluation of Reactivity of the Novel Enediyne and its Sulfoxide: DSC and Computational Analysis.

To better tune the thermally triggered cyclisation experiments to be carried out in the presence of a proton donor, we wished to determine the cyclisation temperature of compounds **71** and **72**. This *datum* is routinely acquired *via* a technique known as Differential Scanning Calorimetry (DSC). Typical profile of such analysis is given in Figure 3.17, which represents the thermal behaviour of compound **71**. An accurately weighted sample of the compound is placed into a furnace and the temperature is raised. The temperature ramp is normally manageable through a computer interfaced to the instrument. The instrument is capable to detect any exothermic or endothermic process taking place inside the furnace. In the case of enediynes, upon cyclisation and formation of the biradical, an endothermic radical polymerisation is observed (hump). The sample is usually run twice to confirm that bulk polymerisation has occurred and there are no further thermal processes going on (straight line).

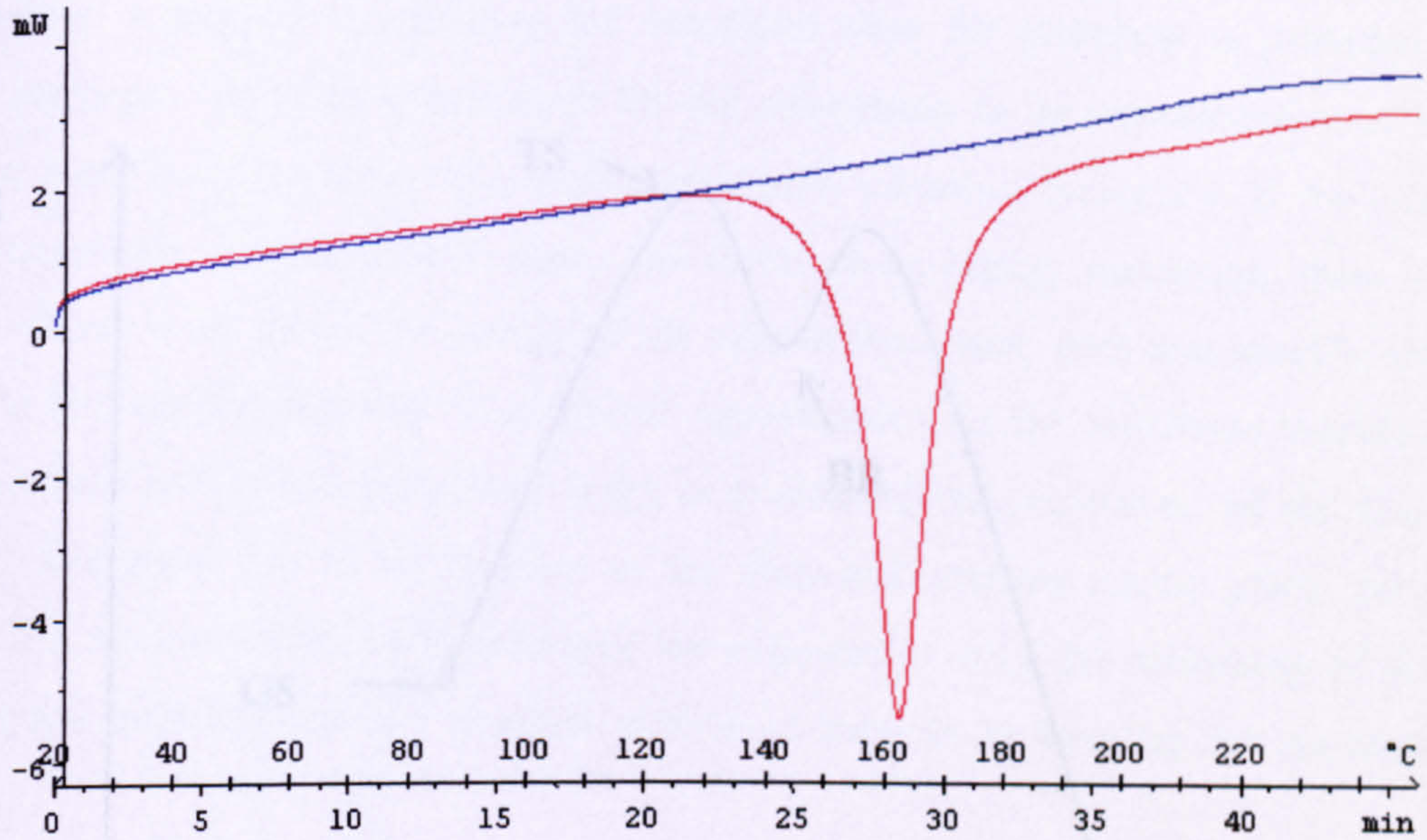


Figure 3.17

The onset temperature (OT) for **71** was found at around 130 °C. The same analysis performed on compound **72** gave an OT of 150-151 °C. Such a large difference in cyclisation temperature going from **71** to its monoxide **72** was somewhat unexpected; most strikingly, the trend was opposite to our expectations. We foresaw an increase in reactivity (i.e lowering of the OT) due to either the contraction of the *cd* distance or the increased strain caused by an element of asymmetry. Both phenomena seemed quite obviously to have arose according to crystallographic data.

This result confirmed what was already strongly hinted at in the literature:

1. Nicolaou's assumption, in which he relates reactivity to *cd* distance, is a very rough approximation. It can be possibly used only to predict weather enediynes are stable at room temperature.
2. Knowledge of the ground state strain energy of enediynes is not enough to predict their reactivity. Such evaluation has to be made based on the difference in energy between transition state and ground state.

To confirm the latter point we decided to run some computational calculations. This is in principle not an easy task. It has already been mentioned that no one to date has been able to reliably calculate the strain energy of the transition state as such. Nevertheless by evaluating the energy of the intermediate (biradical) or the product instead, many authors have been able to match their calculation with the experimental data. Figure 3.18 is a very pictorial representation of the reaction pathway and most likely nowhere near to reality; yet it will help understand the kind of approach and the approximations we have made.

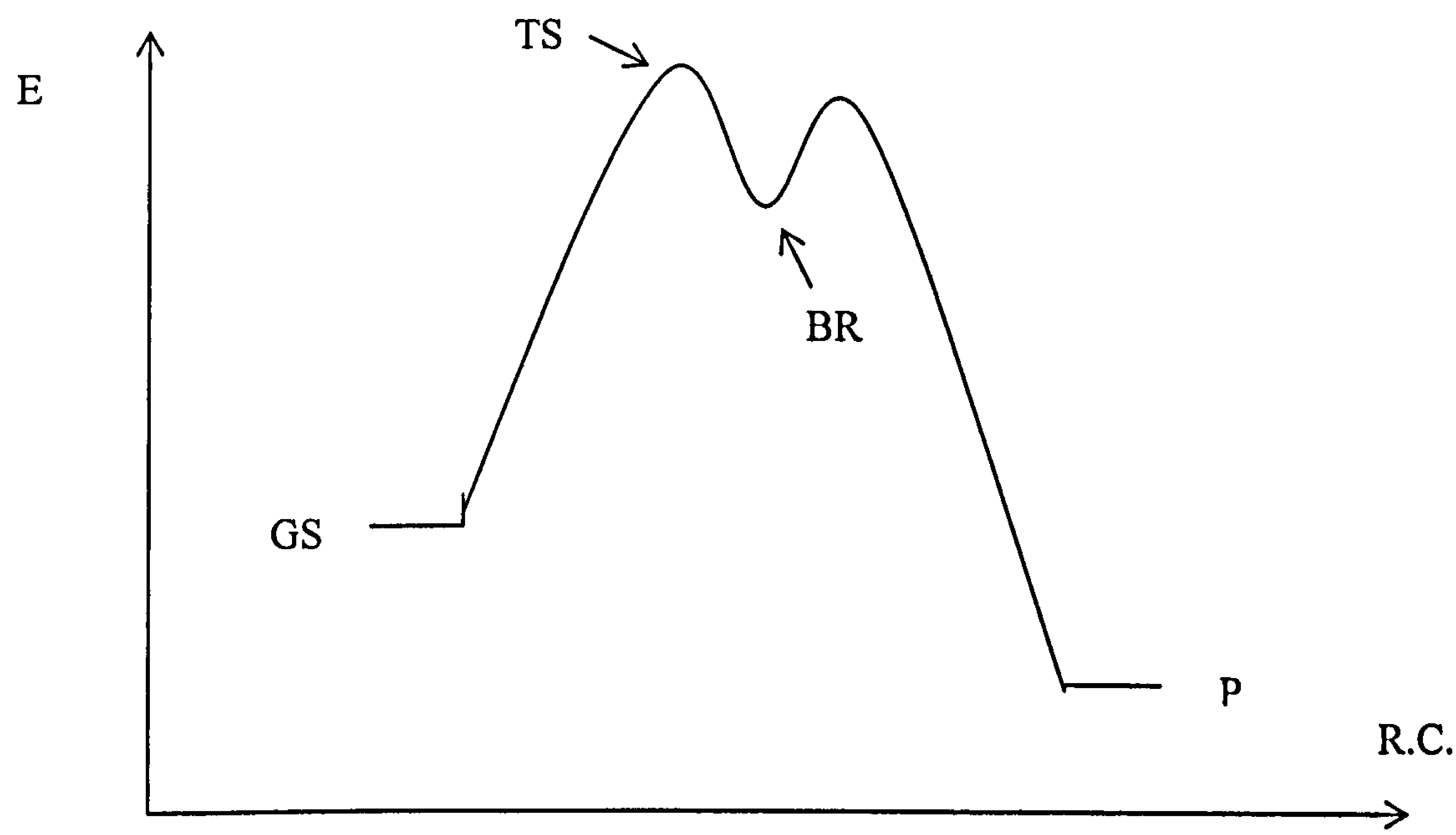


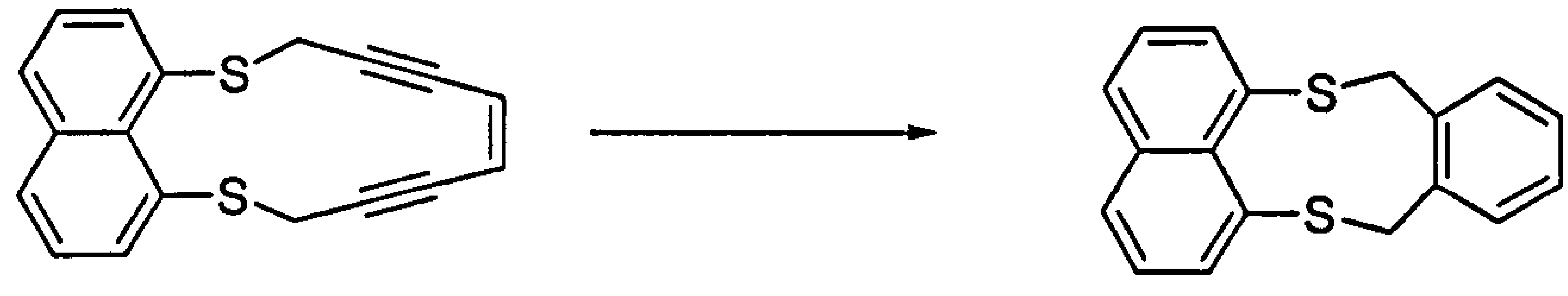
Figure 3.18

It has already been mentioned that strictly speaking Snyder and Magnus' theory relates reactivity to ΔE(Transition State-Ground State).[24] When first introduced, it was assumed that ΔE(Product-BiRadical) should be substantially independent of the type of the system studied and therefore considered a constant. Moreover it was hypothesized that ΔE(BR-TS) is very small, the transition state being product-like. Following these arguments it was proposed that ΔE(P-GS), although not being an absolute measure of the energy required to activate the cyclisation, could be used as a comparative value to predict relative reactivity. These approximations proved justified and their broad validity has been tested using all sorts of theoretical approaches (semi-empirical, *ab initio,* molecular modeling).

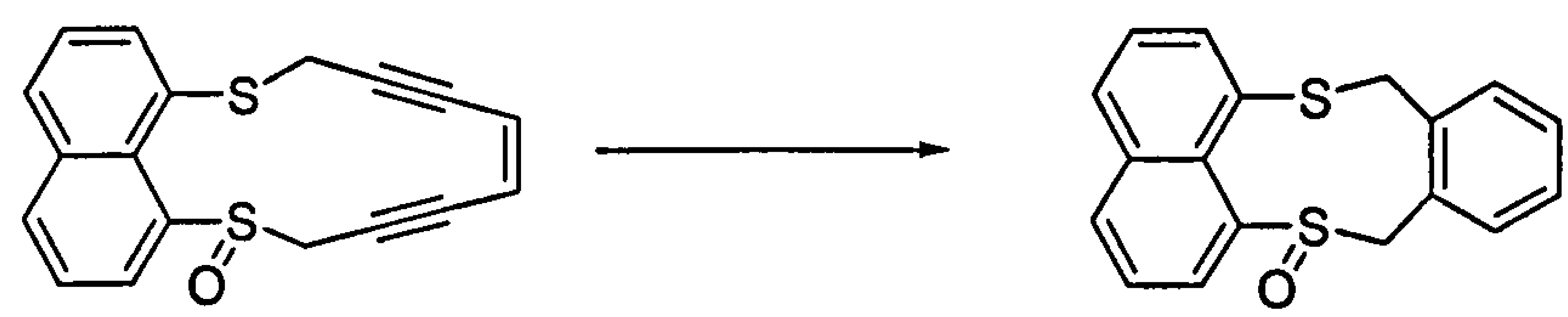
Nowadays the inaccuracy of the aforementioned methods is well established in terms of their intrinsic overestimation or underestimation of the calculated enthalpies of formation of compounds. Nevertheless one may argue that in a purely comparative analysis a non-fluctuating overestimation or underestimation makes no difference at all. One of the most compelling challenges theoretical chemists are faced with is the treatment of multiplicity for the biradical intermediate in calculating the energy of the transition state. None of the methods mentioned above is equipped with a degree of sophistication to deal with such a problem with absolute accuracy.

Nevertheless, a method to calculate the transition state for reactions is provided in the Spartan package. The main requirement for the calculation to be representative of a "real" transition state is the presence of a single imaginary vibration frequency. If the calculated point corresponds to the transition state, and therefore an energy maximum, there must an allowed vibration for which the energy of the system decreases, with that specific vibration relative to the reaction pathway. A graphical representation of the calculated transition state is implemented in Spartan and greatly helps in evaluating the correctness of the result. The indicated frequency has to be relative to the chemical process taking place during the reaction. For the calculation we performed we expected it to be the stretching of the bond being formed between the two terminal acetylenic carbons in forming the six-membered ring.

A doubt is cast, however, regarding the change of multiplicity along the reaction pathway; in our case we are going from a singlet (GS) to a triplet (BR) state. This variation may induce errors in the calculations. We resolved therefore to start our modeling by calculating the energy of the starting materials (**71** and **72**) and the energy of the corresponding products, after hydrogen abstraction (Scheme 3.26). We chose a semi-empirical method to start with, because of its CPU time efficiency.



71 (GS) 89 (P)



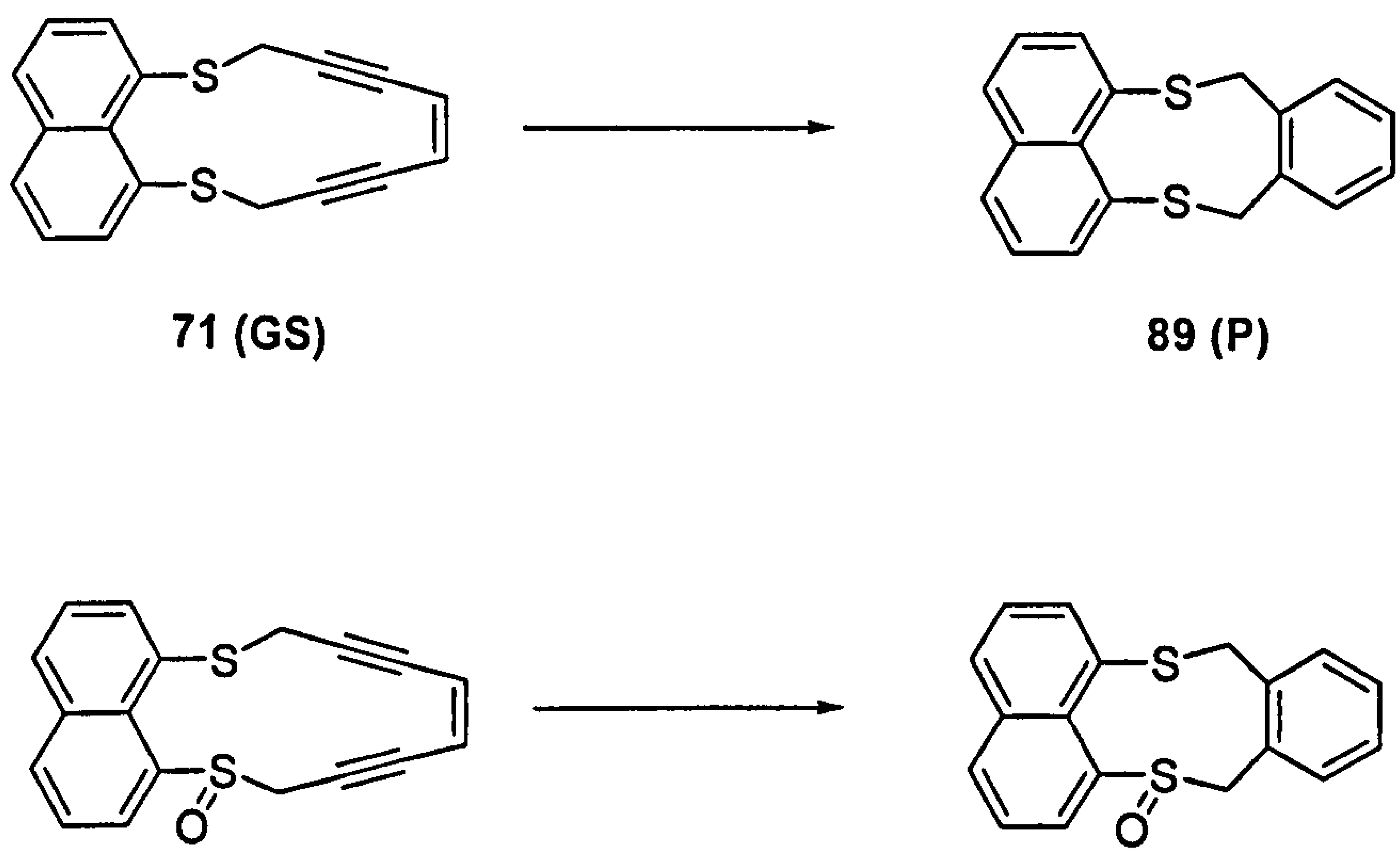
72 (GS) 90 (P)

Scheme 3.26

Running geometry optimisation jobs, the computed enthalpy of formation (H_f) for **89 (P)** was 87.2 Kcal/mol and for **71 (GS)** was 160.3 Kcal/mol, thus ΔE(P-GS) = -73.10 Kcal/mol. H_f for **90 (P)** was 59.8 Kcal/mol and for **72 (GS)** was 133.85 Kcal/mol, thus ΔE(P-GS) = -74.05 Kcal/mol. A Frequency Analysis confirmed all the values as positive, therefore asserting the geometries of the molecules as real *minima* rather than as transition states. The products are lower in energy than the starting material. This means that in both cases ΔE(P-GS) is a negative quantity. Because of this a compound with "less negative" ΔE is supposed to have a higher activation energy. The calculations did not match the experimental results, where the cyclisation temperature of **71** was higher than that of **72**. This might be due to either the limited degree of accuracy of the semi-empirical approach or to the inherent errors introduced by calculating ΔE(P-GS) rather than ΔE(TS-GS).

In order to check that Mayer's assumption (that the hydrogen abstraction is isoenergetic, in spite of the system in study) was correct, we calculated the energy of the biradical intermediates of **71** and **72**. For the two systems this value [ΔE(P-BR)] was virtually identical (105.6 and 105.4 Kcal/mol, respectively), and as expected a highly exothermic process.

We therefore tried to use a more accurate approach than the semi-empirical one, such as Density Function Theory (DFT). This is a method that uses the electron density, rather than the wave function, to represent the total energy of a collection of atoms. The geometric description obtained are sometimes more accurate than using high-level *ab-initio* calculations (CASSCF or CASSCF-PT2), provided one fulfills a number of criteria.[80]



71 (GS) 89 (P)

72 (GS) 90 (P)

Scheme 3.26

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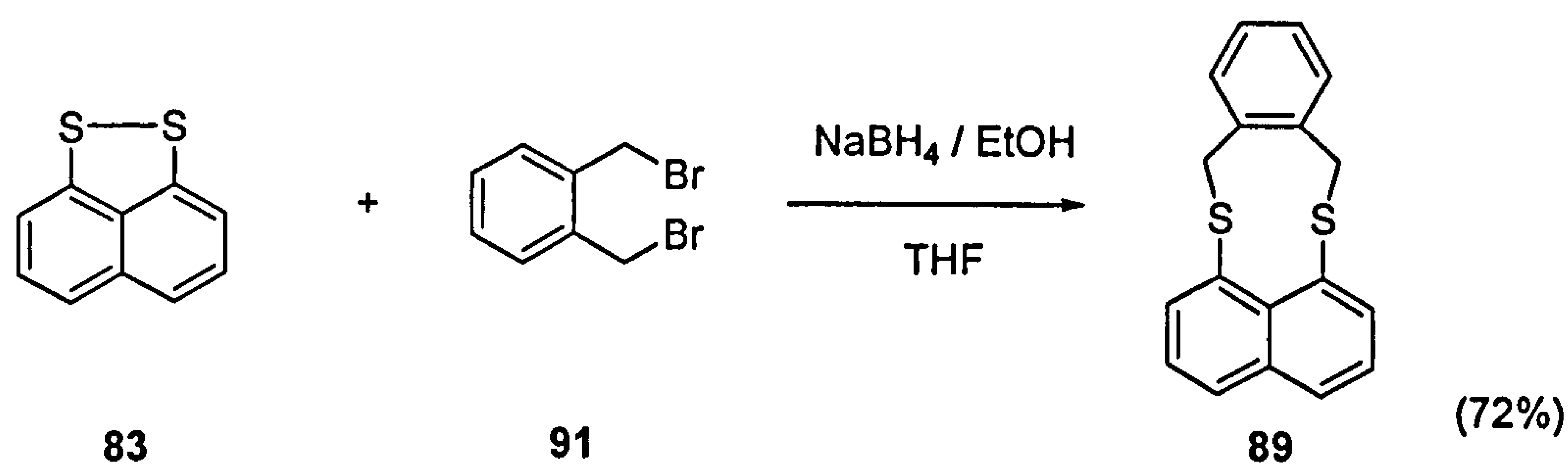
However the size and the complexity of the molecules in this study were too daunting a task for the platform in which we were running the calculations; thus this approach had to be abandoned.

Similar negative results were obtained trying to calculate the energy of the transition state, using the methodology provided in the Spartan package. A series of maxima were found, but none of them was relative to the cyclisation process we sought.

These results showed that in order to predict and confirm relative reactivity of complex enediynes a more tailored theoretical approach must be adopted. The ability to perform such calculations was beyond our ability, possibility and scope, ultimately.

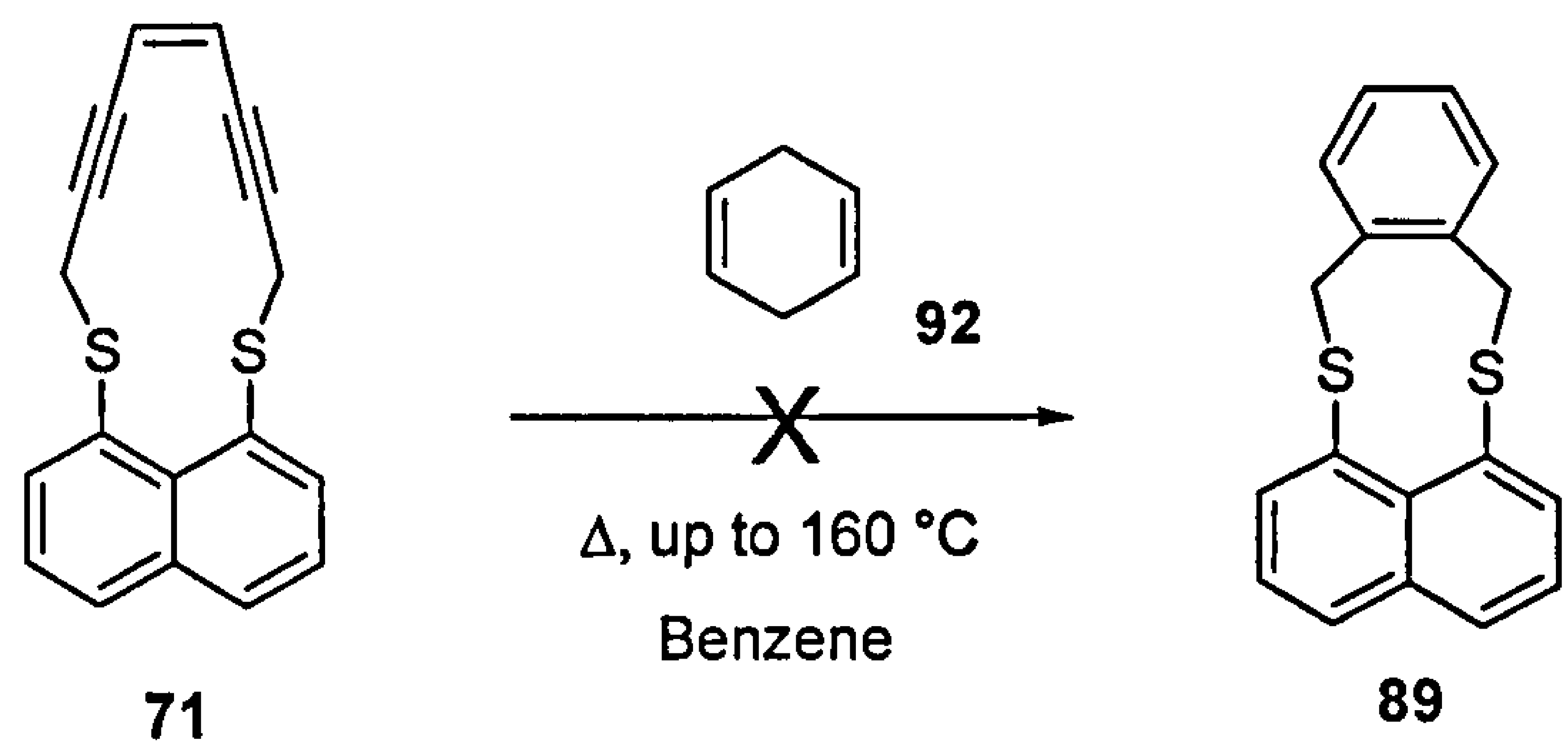
3.3.6. Thermally Triggered Bergman Cyclisation.

With compounds **71** and **72** in our hands, we then proceeded to explore our original idea of exploiting the peri-peri interactions to facilitate cyclisation. We first wanted a pure sample of the cyclisation product for **71**, to compare spectroscopic data and to use a reference in TLC analysis (Scheme 3.27). Using the same rationale employed to assemble **71**, **89** was obtained in good yield.



Scheme 3.27

Then first experiment we attempted was a simple thermally triggered cyclisation. Enediyne **71** was dissolved in benzene and placed in a sealed tube in the presence of 10 equivalents of a hydrogen donor, 1,4-CHD **92**. DSC analysis had indicated an OT of 130 °C. However, **71** had shown already scarce stability at room temperature, therefore we decided to raise the temperature stepwise. The mixture was heated for several hours at 70, 90, 120 and 160 °C but only decomposition was observed (Scheme 3.28).



Scheme 3.28

The same reaction was then attempted in THF; heating the mixture at 160 °C for two hours gave mostly decomposition and few products. Column chromatography permitted only a partial separation. One of the fractions, however, contained the target compound **89** (^{1}H NMR) mixed with other products. It is reported that isopropanol can be used as an alternative source of hydrogen atoms in the Bergman cyclisation.[19a] It has the advantage of being much cheaper than CHD and therefore reactions can be run in it neat. A solution of **71** in isopropanol was heated in a sealed tube for 3 hours at 160 °C. When a TLC analysis was carried out, we noticed that there was starting material left and a lot of products. The sample of **73** we used for a reference also showed a new spot, with an R_f exactly matching the major spot of the reaction. We therefore suspected that compound **89** might have been unstable and although being formed in the reactions we previously attempted, could have disappeared due to decomposition. Indeed, a sample of **89** heated at 120 °C decomposed quite rapidly.

We therefore decided to trap the biradical with 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO), hoping the product would have been more stable. The reaction was carried out at 160 °C in THF and in the presence of five equivalents of TEMPO but only led to decomposition.

3.3.7. Peri-Peri Interaction to Trigger the Bergman Cyclisation.

As mentioned in Paragraph 3.4.1., formation of a dication and the subsequent sulfur-sulfur bond is achievable using a chemical oxidant. A solution of **71** in isopropanol was treated with two equivalents of $NOBF_4$ and stirred for several hours. Many products were obtained and separated. Although some of them revealed new signals in the aromatic region, no **90** was detected. The experiment was repeated on an NMR scale. A sample of **71** was dissolved in a 50:50 mixture of $CDCl_3$:CDCN and the ^{1}H NMR was run. The solution was then poured into a vial containing two equivalents of $NOBF_4$ at zero degrees. The solution turned orange. ^1H NMR revealed the presence of a new set of aromatic protons. Column chromatography yielded 30% of **72**. This hinted at the possible formation of the dication and subsequent oxygen trapping (moisture, air?); nonetheless this event was not enough to trigger spontaneous cyclisation. The alternative method we envisaged to promote sulfur-sulfur bond formation was the treatment of sulfoxide **72** with a strong protic acid or triflic anhydride. Treatment of **72**, even at low temperatures, with concentrated sulphuric acid led exclusively to decomposition products. Also, dissolving a sample of **72** in D_2SO_4 and running the ^1H NMR gave no conclusive results.

We then tried to exploit metal complexation to modify the reactivity of molecule **71**, in the same fashion achieved by Basak.[38] We prepared three NMR samples with **71**:silver triflate ratios of 1:1, 1:2 and 2:1. In spite of the known thiophilicity of silver salts none of the mixtures showed shifting of the proton signals compared to **71**, thus indicating no effective binding.

Finally, we resorted to photochemical methods to trigger the cyclisation of **71**, in line with the work of Furukawa.[71] A solution of **71** in DCM was first irradiated with a 400W high-pressure Hg lamp. Decomposition of the starting material took place and no characterizable compound was isolated, but for disulfide **83**. This again pointed at the effective interaction between the heteroatoms at the *peri*-positions. The reaction was repeated in THF, in the presence of five equivalents of the hydrogen donor CHD. Again the only characterizable products were derived from a sulfur-sulfur bond formation process: namely, disulfide **83** and the corresponding thiosulfinate (see Chapter 1, compound **52**). Careful monitoring of the reaction every ten minutes confirmed the formation of only these two products, along with formation of a solid. The latter would not dissolve in diethyl ether, petroleum ether, dichloromethane, acetonitile or ethanol, thus confirming its polymeric nature. A mixture of the same composition was then irradiated with a 16 W low-pressure Hg lamp. Polymerization occurred almost quantitatively and only traces of disulfide **83** were recovered. Running the reaction in neat isopropanol (400 W, Hg lamp) as hydrogen donor gave similar results. We also tried a photochemical reaction of **71** in chlorobenzene in the presence of the radical species TEMPO, obtaining **83** again as the only characterisable product. We have demonstrated that in the novel compound **71**, bond formation can be achieved both chemically and photochemically. Unfortunately the event seems not to be able to trigger spontaneous cyclisation of the enediyne, or if it does, the products are too unstable to be isolated.

3.3.8. Design of Series of Sulfur-Containing Cyclic Enediynes.

The successful synthesis of **71** encouraged us to expand the scope of the project. We foresaw that by using the same disconnection approach (i.e. coupling dibromo enediyne and commercially available or readily synthesised dithiols) we could prepare a series of sulfur containing macrocyclic enediynes. Their cyclisation temperatures would be determined again via DSC and their relative reactivity would be compared against the calculated ΔE(P-GS) or ΔE(BR-GS).The molecules we intended to prepare are those in Figure 3.19.

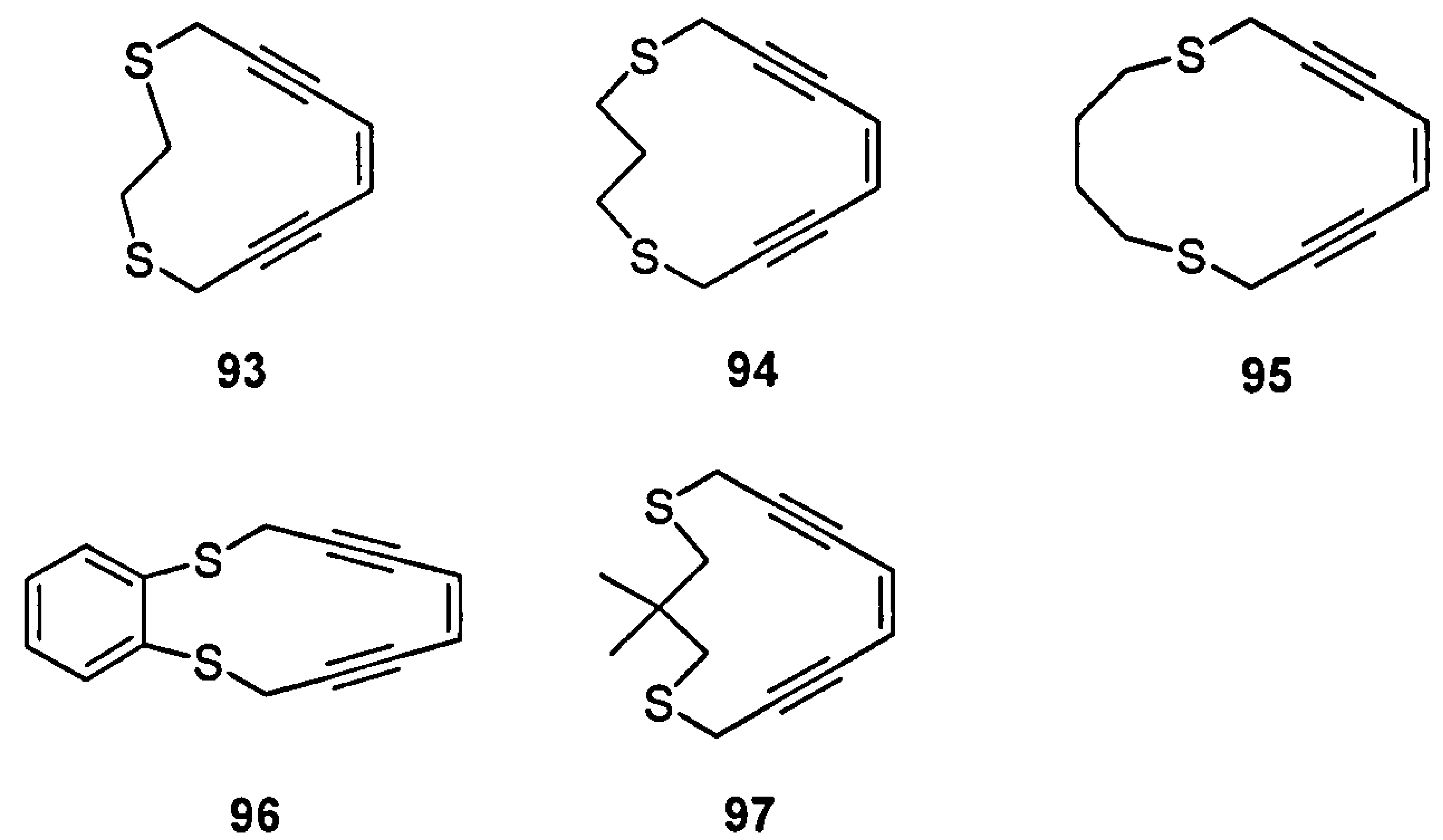
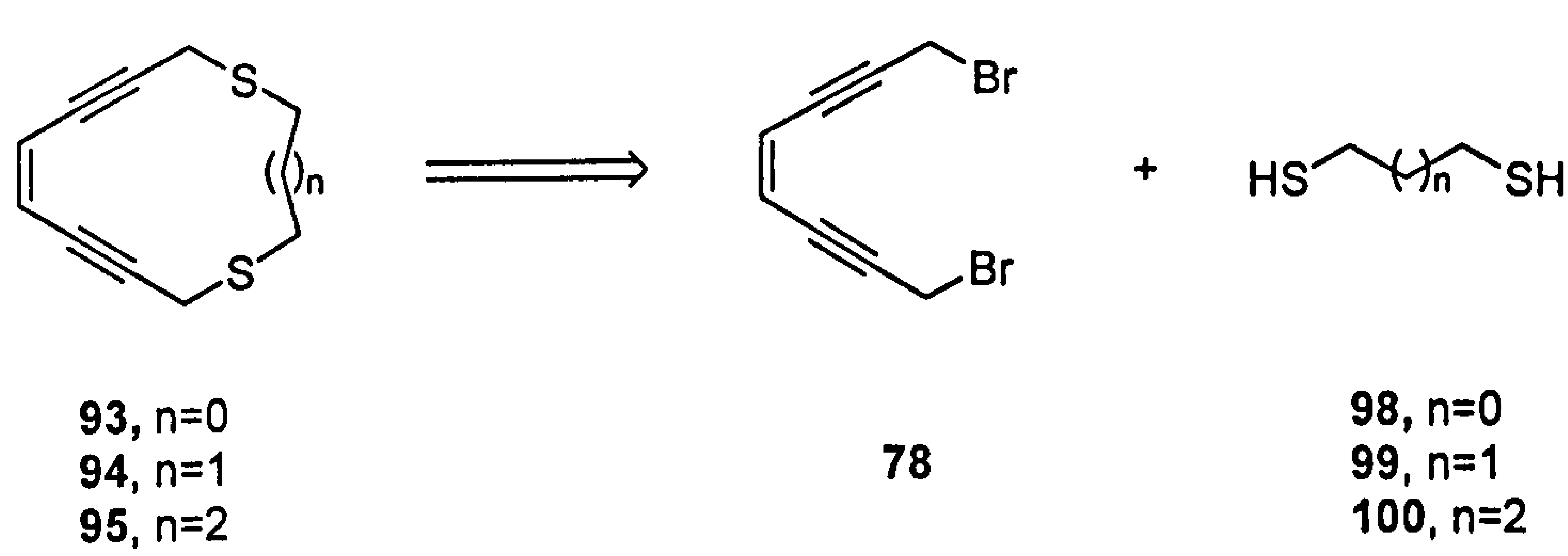


Figure 3.19

The rationale behind this particular selection is as follows: molecules **93, 94** and **95** are homologues. The dithiols necessary for their preparation (**80, 81** and **82**) are all commercially available (Scheme 3.29).



Scheme 3.29

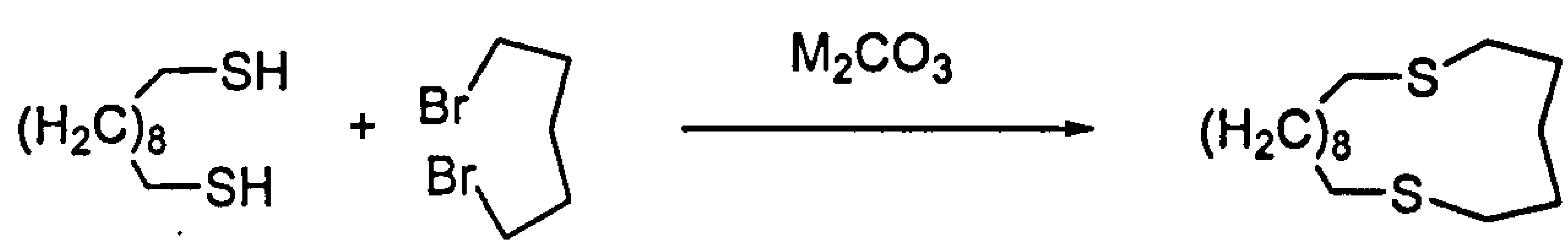
Molecule **97** has an interesting feature represented by the presence of the geminal dimethyl groups. According to the Thorpe-Ingold effect,[81] the steric repulsion between the two substituents should induce a distortion in the tetrahedral geometry of the quaternary carbon, so bringing the two sulfur atoms closer. The effect of this strain and the theoretical shortening of the *cd* distance should impose on this molecule different reactivity compared to that of **94**.

In molecule **96** the chain length equals that of **93** but the hybridization of the bridging carbons is no longer sp^3; this also means that the size of the ring is slightly smaller. Moreover the two sulfur atoms are forced in close proximity by the presence of the aromatic ring, in a similar fashion to that of **56** and **57**. The molecule therefore should experience a certain degree of strain.

3.3.9. Synthesis of a Series of Novel Sulfur-Containing Cyclic Enediynes.

We first tried to prepare **94** to test the general validity of the synthetic strategy. The conditions we used to assemble **71** were not completely appealing because of the low yields obtained. Moreover, in the case of **71** we never isolated dithiol **79**, but we generated it *in situ* by $NaBH_4$ reduction of **83**. We therefore sought an alternative route.

A convenient way to synthesise thia-crown ethers has been proposed by Kellogg and Buter.[82] It exploits base-promoted co-condensation of dithiol **101** with alkyl dihalide **102** in DMF (Scheme 3.30).

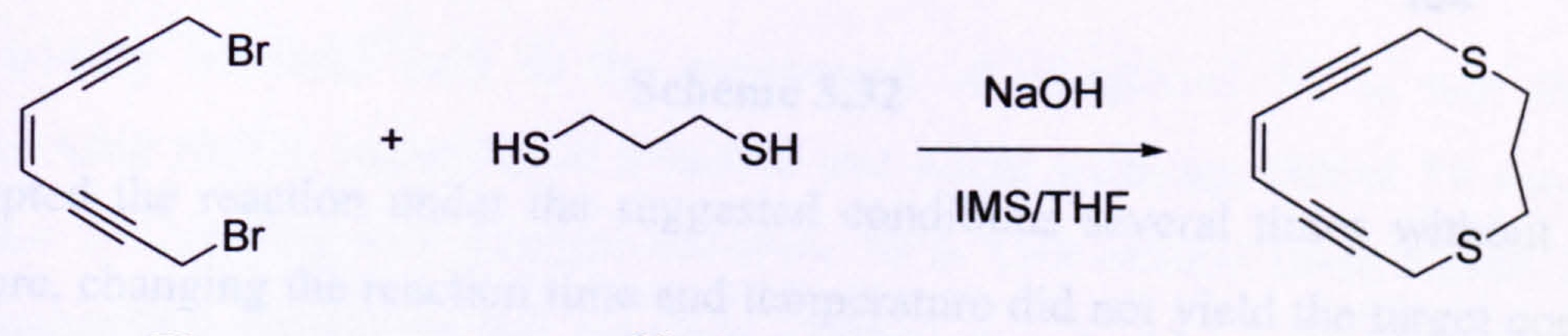


101 **102** **103**

Scheme 3.30

The best yields were obtained using cesium carbonate as base. This has been ascribed to the ability of the cesium thiolates to remain in solution as solvent-separated ion pairs and therefore to improve the reaction solubility characteristics.[83] Following the original paper[82] and a modified procedure[83], condensation of dithiol **101** with enediyne **102** could not be achieved; modifications of some parameters, such as solvent, reaction temperature and base of choice, also met with failure.

The synthesis of **103** was instead accomplished following a procedure by Went (Scheme 3.31).[84]



Scheme 3.31

Indeed by running the reaction in a 9:1 mixture of IMS:THF the isolated yield for **94** was very satisfactory (70%). We succeeded in growing crystals of compound **94** by slow evaporation of its dichloromethane solution in a hexane atmosphere. Figure 3.20 shows the corresponding X-ray analysis (in the lateral view protons are omitted for clarity).

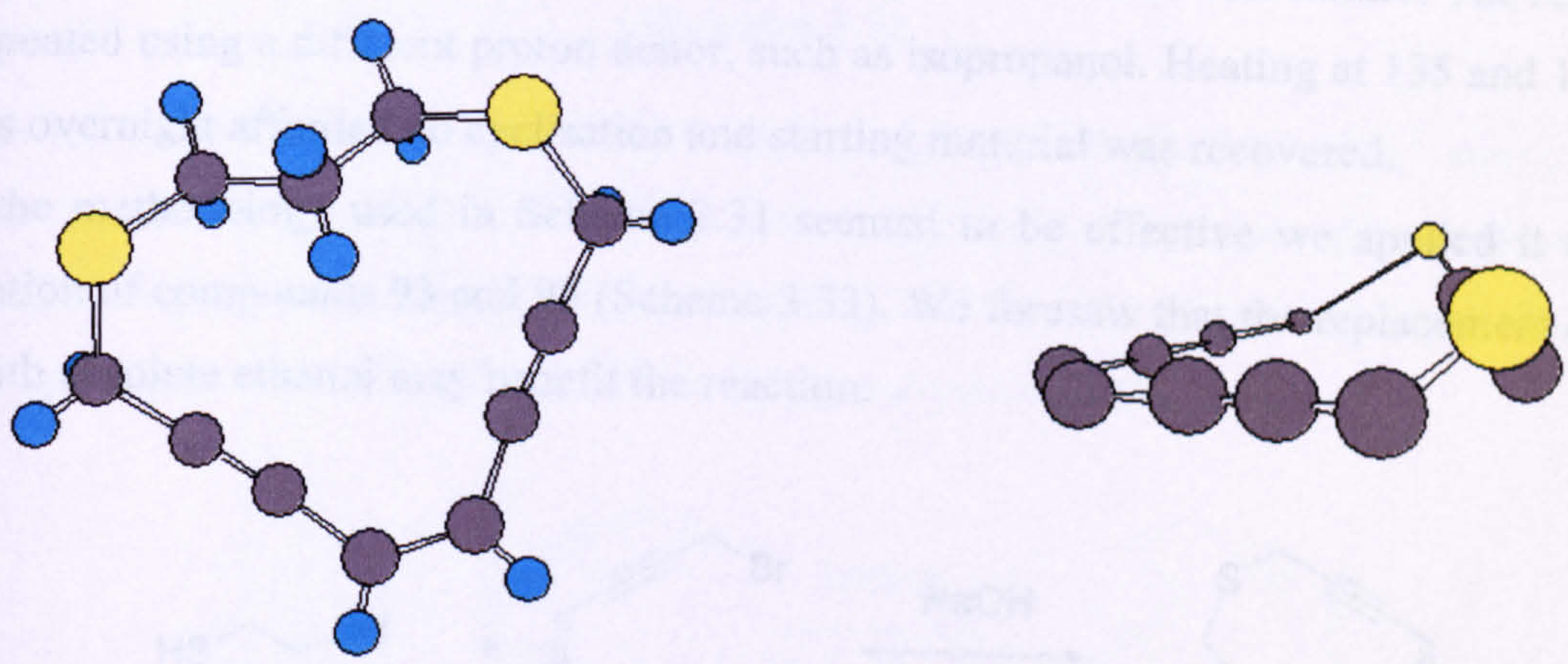
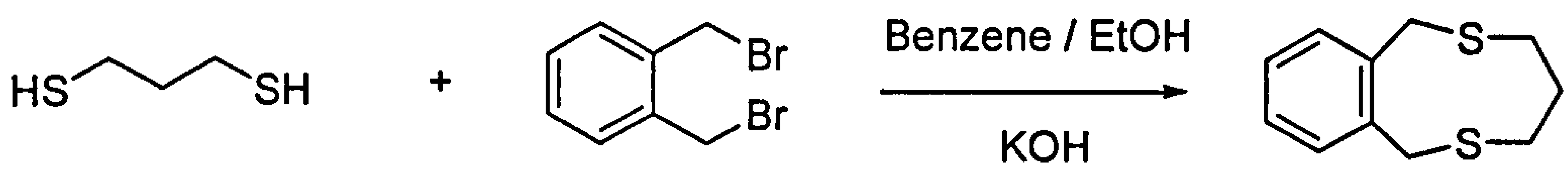


Figure 3.20

The structure does not have many points of interest. The *cd* distance (4.573 Å) is well above the suggested limit for stability at room temperature. The acetylenic bonds are only slightly out of linearity (178 degrees) and the two sulfur atoms are both sitting above the plane of the enediyne moiety.

Before trying to induce thermal cyclisation we decided to synthesize the cyclisation product, which is a known compound (Scheme 3.32).[85]



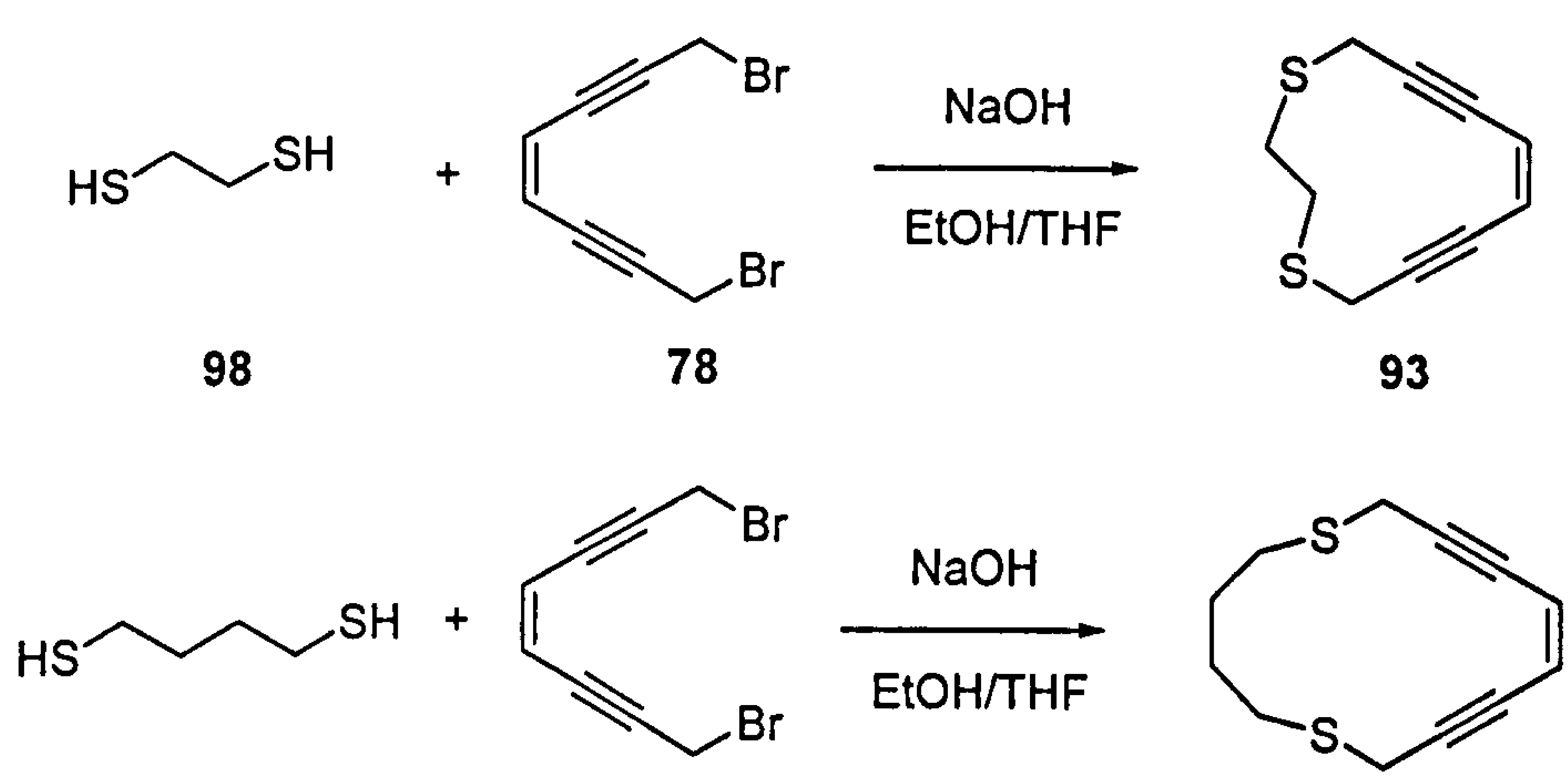
99 91 104

Scheme 3.32

We attempted the reaction under the suggested conditions several times without success. Furthermore, changing the reaction time and temperature did not yield the target compound. Adopting the same solvent mixture that was successful in synthesizing **89** also did not give a positive result. We found an alternative preparation that makes use of the same reagents as in Scheme 3.32 but mimics Butler's approach.[86] Carrying out the reaction in DMF and using $CsCO_3$ as base, **104** was prepared in 43% yield.

DSC analysis of **94** showed a cyclisation on-set temperature of 105 °C. Nevertheless, heating a solution of **94** in benzene at 120 °C in the presence of 10 equivalents of CHD gave no reaction at all. Raising progressively the temperature to up to 160 °C only led to decomposition. Refluxing the same mixture in mesitylene also met with failure. The reaction was repeated using a different proton donor, such as isopropanol. Heating at 135 and 160 °C degrees overnight afforded no cyclisation and starting material was recovered.

Since the methodology used in Scheme 3.31 seemed to be effective we applied it to the preparation of compounds **93** and **95** (Scheme 3.33). We foresaw that the replacement of the IMS with absolute ethanol may benefit the reaction.



98 78 93

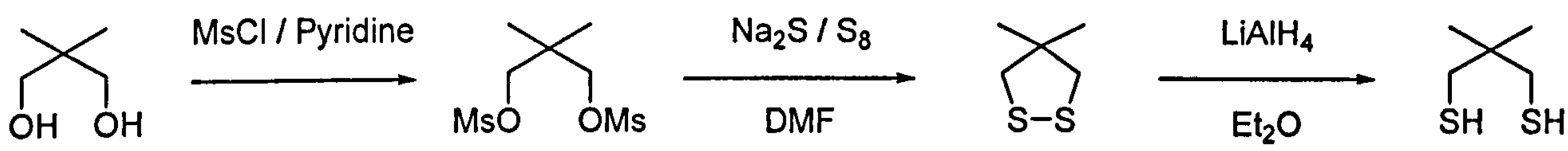
100 78 95

Scheme 3.33

Indeed the target compounds were synthesized in good yields (78% and 73%, respectively). Thermal cyclisation was attempted on compound **93**. The enediyne was stirred in the presence of 10 equivalents of CHD, at temperatures ranging from 40 °C degrees to reflux for several hours; samples were analysed by ^{1}H NMR at regular intervals. After 40 hours the substrate had decomposed.

Out of curiosity we went back to the preparation of compound **71**, to test these new conditions. After $NaBH_4$ reduction of disulfide and acidic work-up, dithiol **79** was isolated (see Chapter I). Coupling with dibromo-enedyine **78** in THF-ethanol using NaOH as a base was successful but inferior to the previous method as was the use of a different base (pyridine) in both ethanol and THF.

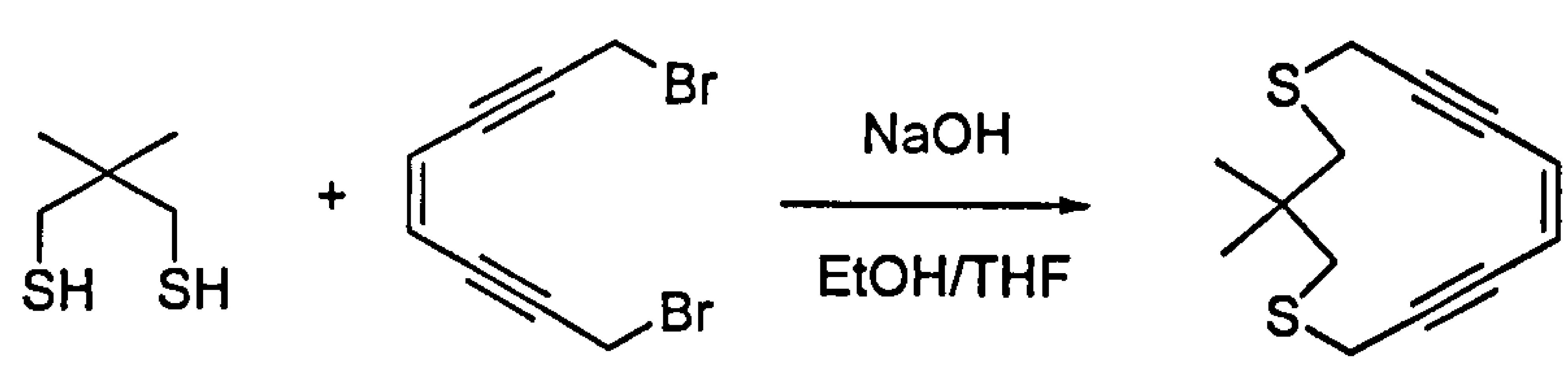
In order to prepare of cyclic enediyne **97** dithiol **108**, a known compound, had to be synthesised (Scheme 3.34).[87]



105 **106** **107** **108**

Scheme 3.31

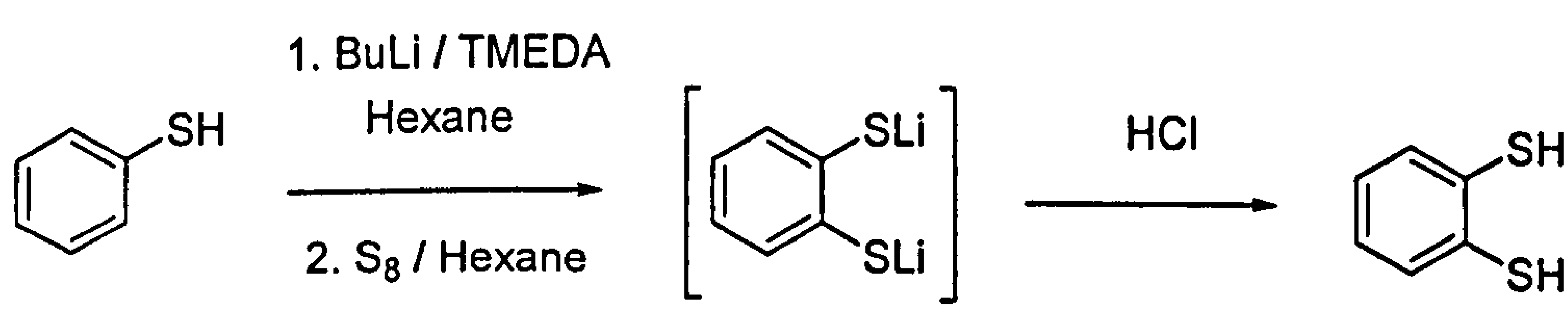
After mesylate activation of the diol **105**, trapping of the the in-situ formed S_2^{2-} species gave the five-membered heterocycle **107**. The latter was easily reduced to the corresponding dithiol **108** in good overall yield (77%). Coupling of **108** with dibromoenediyne **78** under Went's conditions smoothly afforded **97** in very good yield (91%).



108 **78** **97**

Scheme 3.35

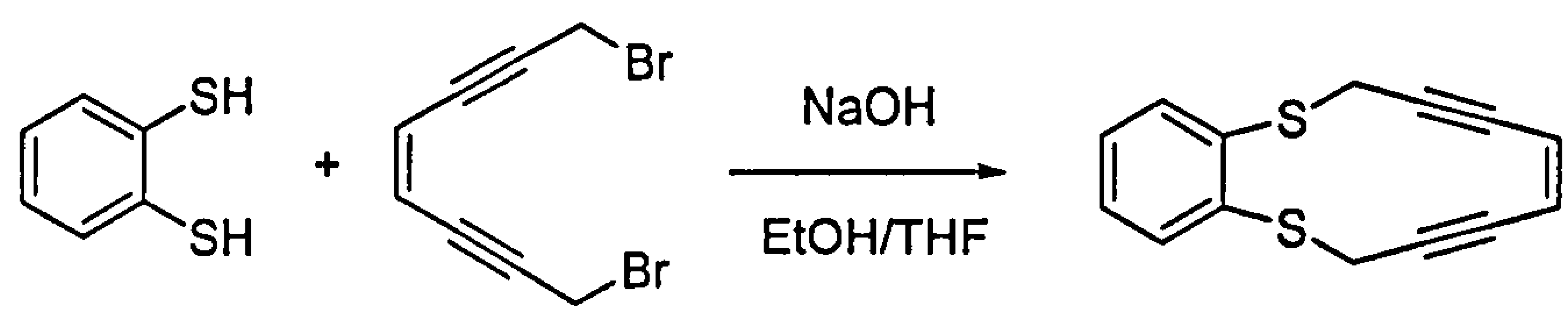
Finally, we prepared dithiol **111** (Scheme 3.36).[88]



109 **110** **111**

Scheme 3.36

TMEDA-assisted ortho lithiation of thiophenol **109** and quenching with elemental sulfur afforded **111** (75%). Formation of the corresponding cyclic enediyne proved slightly more capricious than for the previous examples but finally furnished **96** in 58% yield (Scheme 3.37).



111 **78** **96**

Scheme 3.37

3.3.10. Conformational Analysis of the Novel Enediynes.

Having synthesized all the target compounds we measured their cyclisation temperatures with standard DSC analysis (Table 3.1).

COMPOUND	CYCLISATION TEMPERATURE (°C)
93	60
94	105
95	80
96	112
97	90

Table 3.1

Noteworthy is the non-linear trend of the homologues and the effect of the geminal dimethyl substitution (**97**) on the reactivity of enediyne **94**.

The other element we were interested in was the *cd* distance of these new molecules. The most accurate method to extrapolate this information is from crystallographic data. Unfortunately compounds **93** and **95** were oils and for **97** we were unable to grow crystals. Crystals of compound **96** were obtained by slow evaporation of its dichloromethane solution in an hexane atmosphere (Figure 3.21).

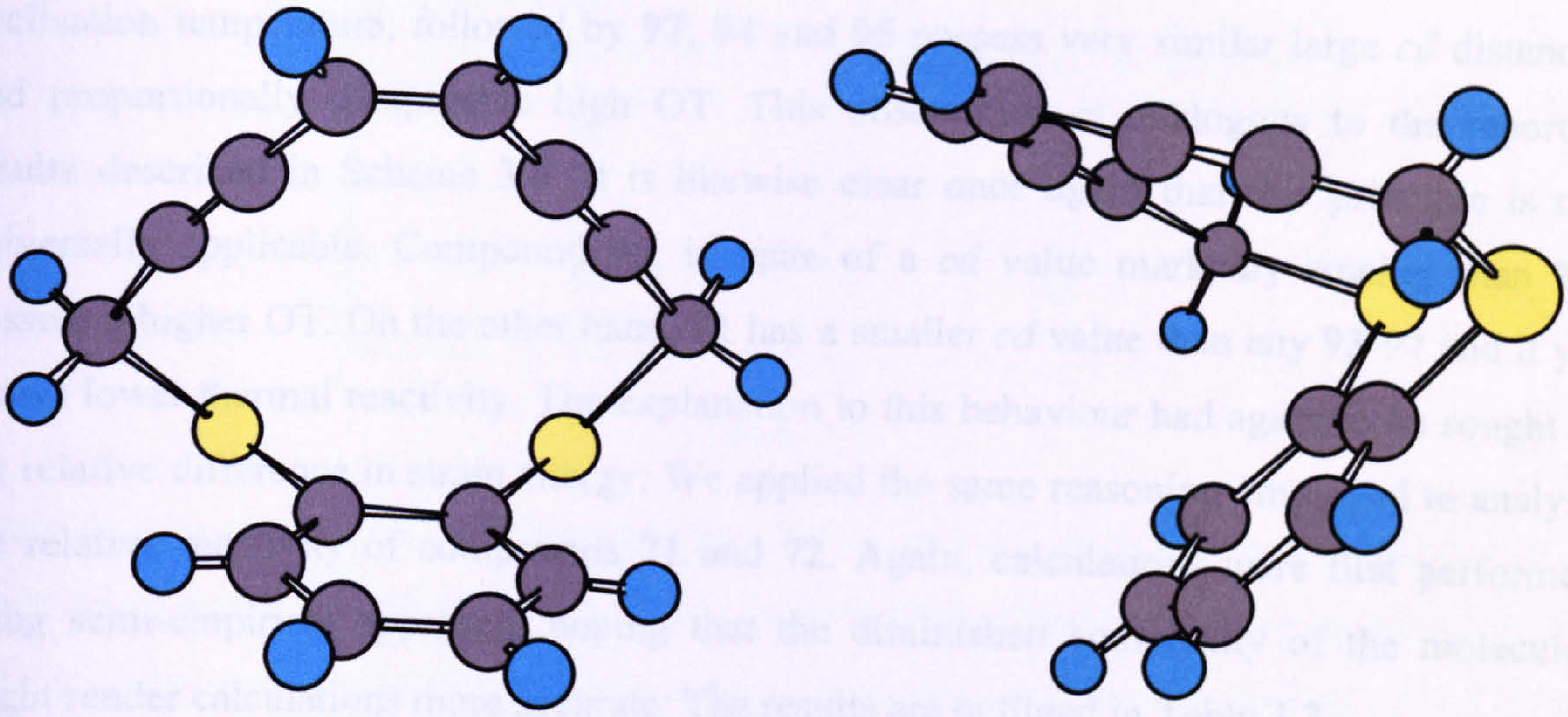


Figure 3.21

The *cd* distance equals 4.213 Å. The two sulfur atoms separation is 3.188 Å, similar to that in **71** or **72** and still within twice the van der Waals radius of sulfur.

An alternative method to determine the *cd* distance parameter is through computational methods. To confirm the validity of this approach we went back to the calculation we had performed on the ground state of enediyne **71** and its oxide **72**. In both cases the calculated *cd* distances were substantially identical to those measured *via* X-ray. The same idea was applied for the other two molecules for which we had obtained crystals, **94** and **96**. Again, there was a more than satisfactory match between experimental and calculated *cd* value. The complete set of *cd* measures is given in Table 3.2. The compounds are listed in progressively increasing order of cyclisation temperatures.

COMPOUND	*cd* DISTANCE (Å)
93	4.02[a]
95	4.18[a]
97	4.22[a]
94	4.573[b] (4.61)[a]
96	4.213[b] (4.22)[a]

[a] Computed value; [b] X-ray data

Table 3.2

A comparison between Tables 3.1 and 3.2 revealed that for simple cyclic enediynes, Nicolaou's principle still held true. If we do not take into consideration compound **96** (different carbon hybridization), the "natural" series **93-97** shows increasing OT as the two acetylenic carbons are set further apart: **93** has the smallest *cd* value and the lowest cyclisation temperature, followed by **97**; **94** and **95** possess very similar large *cd* distances and proportionally comparable high OT. This observation is analogous to the reported results described in Scheme 3.6. It is likewise clear once again that this principle is not universally applicable. Compound **96**, in spite of a *cd* value markedly smaller than **95**, possess a higher OT. On the other hand, **71** has a smaller *cd* value than any **93-97** and it yet shows lower thermal reactivity. The explanation to this behaviour had again to be sought in the relative difference in strain energy. We applied the same reasoning employed to analyse the relative reactivity of compounds **71** and **72**. Again, calculations were first performed using semi-empirical approach, hoping that the diminished complexity of the molecules might render calculations more accurate. The results are outlined in Table 3.3.

COMPOUND	ΔE(P-GS) (Kcal/mol)
93	-89.9
95	-87.5
97	-88.7
94	-82.3
96	-87.6

Table 3.3

The mismatch is obvious as we were expecting progressively "less negative" values. The results did not became any better when we calculated ΔE(BR-GS). Results are shown in Table 3.4.

COMPOUND	ΔE(BR-GS) (Kcal/mol)
93	18.2
95	20.6
97	19.3
94	25.3
96	20.3

Table 3.4

A sharply improved correlation arose form the values calculated for ΔE(TS-GS). In spite of the question mark represented by the singlet-triple transition, all the maxima we found bore only one imaginary frequency, relative to the ring closure process (Table 3.5).

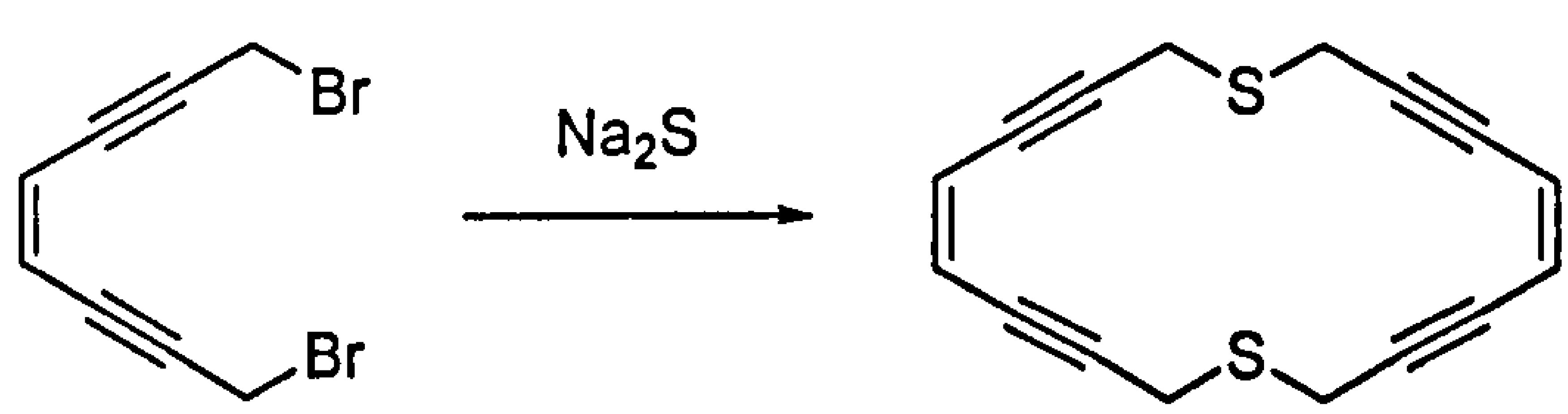
COMPOUND	ΔE(TS-GS) (Kcal/mol)
93	65.8
95	81.7
97	87.1
94	88.3
96	90.0

Table 3.5

These results seemed to underline that the "strain energy" approach is a valuable one in predicting thermal behaviour of enediynes. Nevertheless, extreme care has to be put on the choice of the mathematical tools one employs. Semi-empirical calculations of ΔE(P-GS) on all the systems in this study have failed to deliver a satisfactory output. On the other hand, the computation of the transition states, in spite of being extremely demanding in terms of CPU time, gave the correct correlation with experimental data. Nonetheless this approach has to be carefully pondered; its applicability has to be further tested to confirm its reliability.

3.3.11. Synthesis of a Novel Macrocyclic bis-Enediyne.

We had already tried to bind **71** to a silver cation to exploit metal-complex tuned cyclisation, but negative results might have due to the limited size of the cavity. We therefore considered sulfur-containing bis-enediyne **112** (Scheme 3.38). We envisaged that the large number of unsaturation centres and the presence of the sulfur lone pairs would have made **112** an ideal candidate for metal complexation. Also appealing was the fact that **112** could be readily prepared in one step from **78** (Scheme 3.38).



78 **112**

Scheme 3.38

Yields using ethanol as a solvent were very poor (10%). Slightly better results were achieved by pre-absorbing the sodium sulphide on alumina.[89] Using conditions reported elsewhere,[90] yields improved dramatically, both using non-supported (40%) and supported sodium sulphide (45%). The solvent used was a mixture of ethanol:dichloromethane (2:5) and slow addition of a **78** was carried out at zero degrees under dilute solution conditions. The compound was solid; crystals were obtained directly after column chromatography, by slow evaporation of one of the fractions. X-ray analysis is shown in Figure 3.22 (H's are omitted for clarity).

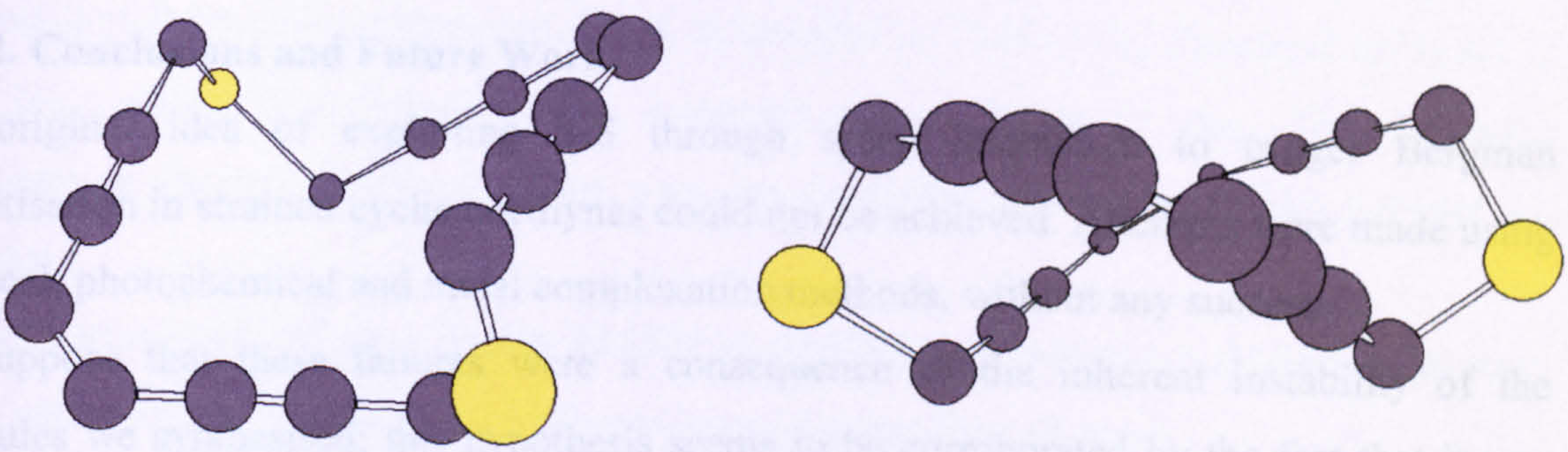


Figure 3.22

Compound **112** adopts a twisted conformation in the solid state, the two enediyne moieties being inclined at an angle of 56 degrees to one another. The enediyne moieties remain almost planar, with a mean deviation of 4.2 degrees from planarity, and a mean *cd* distance of 4.30 Å. As for all the other molecules presented in this chapter we attempted thermal aromatisation. DSC analysis suggested a cyclisation temperature of around 115 °C. Bis-enediyne **112** was therefore heated for more than two days in refluxing toluene in the presence of hydrogen donor CHD. Only starting material was recovered. The cyclisation was also attempted in neat isopropanol at 140 °C, unsuccessfully.

Metal complexation was then attempted by adding 2 equivalents of silver triflate to a solution of **112** in $CDCl_3$. ^1H NMR showed no shift in the peaks. Since the silver salts was scarcely soluble in chloroform, we prepared a solution of silver triflate in CD_3CN of known titre. Then four NMR tubes were prepared containing the same amount of **112** in $CDCl_3$. One was topped up with CD_3CN and to the other three were added aliquots of the triflate solution so as to prepare mixtures of **112**:AgOTf in 1:1, 2:1 and 1:2 ratios. The four samples were submitted for ^1H-NMR. Again, in all four samples the peaks had identical chemical shift.

We finally tried oxidation of **112**, in the same fashion as we did for **71**, to evaluate conformational and reactivity modification by introducing an element of asymmetry. Treatment with one equivalent of *m*-CPBA was attempted in different solvents and at various temperatures. Although the expected perbenzoic acid could be isolated, no other product was obtained.

3.3.12. Conclusions and Future Work.

The original idea of exploiting S-S through space interaction to trigger Bergman aromatisation in strained cyclic enediynes could not be achieved. Attempts were made using chemical, photochemical and metal complexation methods, without any success.

We suppose that these failures were a consequence of the inherent instability of the molecules we synthesised; this hypothesis seems to be corroborated by the fact that it was impossible to obtain cyclisation products under thermal treatment. In most of the experiments decomposition was observed instead.

Negative results in the complexation experiments probably stem from the fact that the sulfur lone pairs are pointing out of the ring. It is known, for instance, that thiacrowns preferably adopt an *anti* conformation rather than a *gauche*. This is due to the rather long sulfur-carbon bonds and the repulsive interaction between sulfur lone pairs. It follows that for metal binding to occur, considerable conformational reordering is required, which is energetically unfavourable.[91]

Nevertheless a reliable synthetic approach to the synthesis of cyclic, sulphur-containing enediynes has been developed. This could be in the future utilised for the preparation of similar compounds designed with enhanced stability and lower cyclisation energetic barriers. Moreover further validation of the theory that relates ease of cyclisation to the difference in strain between ground and transition states has been provided. The computational method utilised may not be strictly reliable (in terms of absolute values) but it is a useful tool for the rapid evaluation of relative tendency of a series of compounds towards cyclisation.

Future work may also be devoted to the design and preparation of molecules with the appropriate geometry and cavity size to bind cations.

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected.

Infra-red spectra were recorded on a Perkin-Elmer Paragon 1000 Fourier transform I.R. spectrometer.

Proton NMR were recorded using a Bruker AM360 or AM400 spectrometer in deuterochloroform, unless otherwise stated, referenced to TMS (δ 0). Chemical shifts are in parts per million (δ ppm). Coupling constants are in Hertz (*J* Hz). The following abbreviations are used: bs-broad singlet, s-singlet, d-doublet, dd-double doublet, t-triplet, m-multiplet.

^{13}C NMR were recorded on a Bruker AM360 or AM400 spectrometer in deuterochloroform unless otherwise stated. Chemical shifts are in parts per million (δ ppm).

Mass spectra were recorded on a Jeol AX505W spectrometer (EI).

Flash chromatography was carried out according to Still's paper[92] using Merck silica gel 60 (4063 μm). *Analytical t.l.c.* was carried out on Merck (aluminium sheets) silica gel 60 F_{254} plates using short wave (254 nm) UV light, Ninhydrin spray (from BDH), $KMnO_4$ or Anisaldehyde to visualise components.

Solvents and reagents were purified as follows:

Benzene - Distilled from calcium hydride and stored over 4 Å molecular sieves.

Butylamine - Distilled from calcium hydride and stored over potassium hydroxide in the dark.

Dichloromethane - Distilled from calcium hydride and stored over 4Å molecular sieves.

Pyridine – Refluxed over calcium hydride and distilled prior to use.

Tetrahydrofuran was freshly distilled from sodium and benzophenone.

TMEDA- Purified by vacuum distillation from P_2O_5.

All other reagents and solvents were used as received.

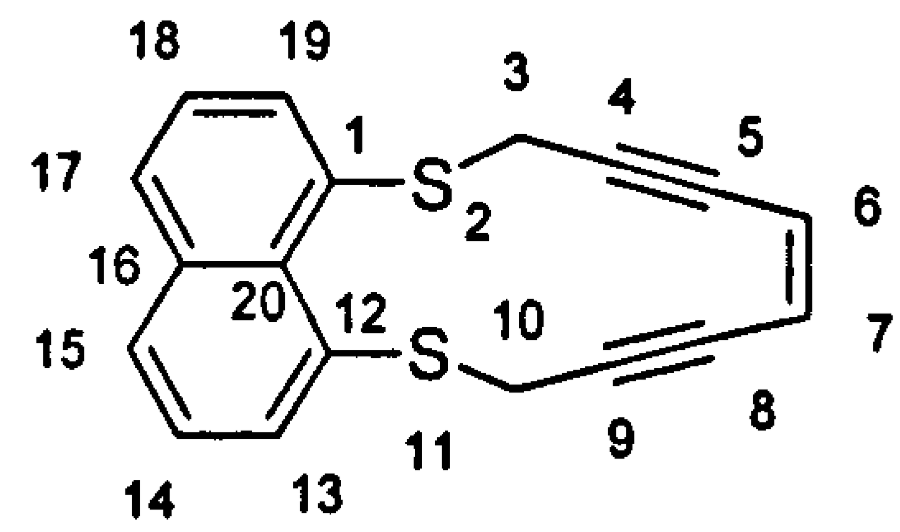
Cooling mixtures were obtained as follows:

0 °C: ice/water.

-5 °C to –78 °C: acetone/dry ice.

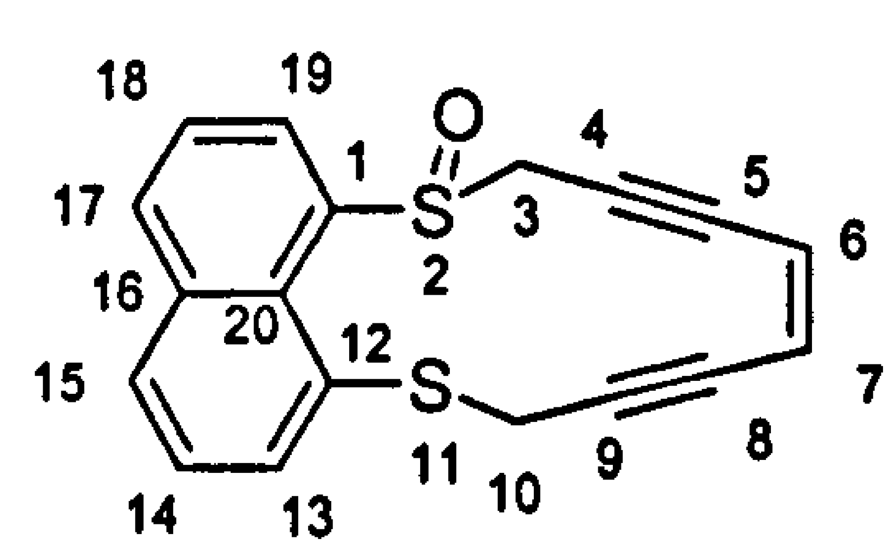
Unless otherwise stated, all reactions in non aqueous media were carried out under an atmosphere of argon in oven-dried glassware.

2,11-Dithia-tricyclo[10.7.1.0^{16,20}]eicosa-1(19),6,12(20),13,15,17-hexaene-4,8-diyne (71).



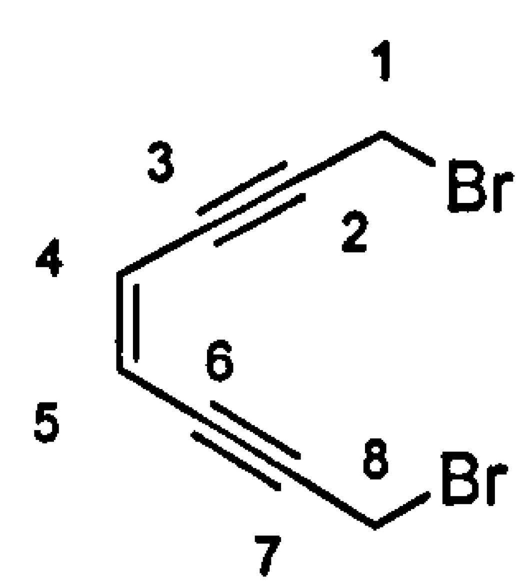
$NaBH_4$ (325 mg, 8.6 mmol) was suspended in ethanol (30 cm^3). To this a solution of [1,8-*c,d*]-1,2-dithiole (190 mg, 3.9 mmol) in THF (50 cm^3) was added dropwise and the mixture was stirred for 30 mins. 1,8-Dibromooct-4-ene-2,6-diyne (1.124g, 4.3 mmol) in THF (30 cm^3) was then added dropwise over 3 h. Once the addition was completed, the reaction was stirred for a further 30 mins and then quenched with water. The mixture was extracted with diethyl ether (3 x 50 cm^3), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (96:4 60-80 petroleum ether:diethyl ether) gave **71** (385 mg, 34%) as a white crystalline solid; R_f 0.32 (95:5 60-80 petroleum ether:diethyl ether); υ_{max} (neat)/cm^{-1} 1593 (Ar), 2361 (C≡C); mp 68-69 °C (dichloromethane); δ_H(400 MHz; $CDCl_3$) 4.00 (4H, s, 3-H and 10-H), 5.60 (2H, s, 6-H and 7-H), 7.41 (2H, dd, *J* 8.0 and 7.2 Hz, 14-H and 18-H), 7.73-7.77 (4H, m, 13-H, 15-H, 17-H and 19-H); δ_C(90 MHz, $CDCl_3$) 28.5 (t, 3-C and 10-C), 82.2 (s, 5-C and 8-C), 94.5 (s, 4-C and 9-C), 120.9 (d, 6-C and 7-C), 125.7 (d, 14-C and 18-C), 129.7 (d, 13-C and 19-C or 15-C and 17-C), 133.1 (s, 16-C), 134.5 (d, 13-C and 19-C or 15-C and 17-C), 135.9 (s, 20-C), 136.3 (s, 1-C and 12-C); *m/z* (LREI) 292 (M^+; 4%), 234 (21), 221 (20), 190 (100), 102 (15); *m/z* (HREI) calcd for $C_{12}H_{14}S_2$ 222.05369; found 222.05339.

2,11-Dithia-tricyclo[10.7.1.0^{16,20}]eicosa-1(19),6,12(20),13,15,17-hexaene-4,8-diyne 11-oxide (72).



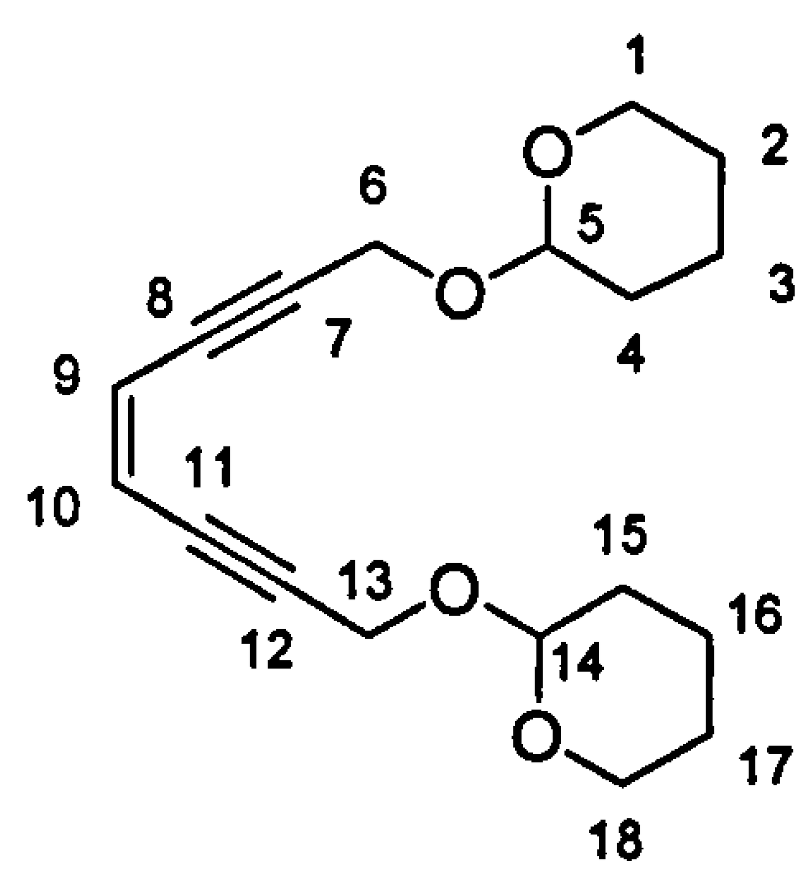
2,11-Dithia-tricyclo[10.7.1.0^{16,20}]eicosa-1(19),6,12(20),13,15,17-hexaene-4,8-diyne (40 mg, 0.13 mmol) was dissolved in dichloromethane (40 cm^3) and the solution was cooled to –60 °C. A solution of *m*-CPBA (25 mg, 0.14 mmol) in dichloromethane (15 cm^3) was added dropwise and the solution was stirred for 2h at the same temperature. The temperature was allowed to rise to –30 °C and the stirring was continued for another hour. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with dichloromethane (3 x 30 cm^3), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (10:90 60-80 petroleum ether:diethyl ether) gave **72** (34 mg, 80%) as a white crystalline solid; R_f 0.1 (50:50 60-80 petroleum ether:diethyl ether); υ_{max} (neat)/cm^{-1} 1085 (S=O), 1589 (Ar), 1673 (C=C), 2193 (C≡C); mp 57-59 °C (dichloromethane); δ_H(400 MHz; $CDCl_3$) 3.88 (1H, ddd, *J* 16.5, 1.1 and 1.1, 10-H_a or 10–H_b,), 4.03 (1H, d, 3-H_a or 3–H_b, *J* 15.9), 4.04 (1H, dd, *J* 16.8 and 1.7, 10-Ha or 10-Hb), 4.18 (1H, dd, *J* 15.8 and 1.9, 3-Ha or 3-Hb), 5.56 (1H, d, *J* 10.1, 7-H), 5.64 (1H, d, *J* 10.1, 6-H), 7.44 (1H, dd, *J* 7.4 and 8.0, 14-H), 7.63 (1H, dd, *J* 8.1 and 7.4, 18-H), 7.69 (1H, dd, *J* 7.4 and 1.3, 13-H), 7.78 (1H, ddd, *J* 8.0, 1.3 and 0.4, 15-H), 7.92 (1H, ddd, *J* 8.1, 1.4 and 0.4, 17-H), 8.49 (1H, dd, *J* 7.4 and 1.4, 19-H); δ_C (100 MHz; $CDCl_3$) 28.77 (t, 10-C), 55.4 (t, 3-C), 84.3, 85.6, 90.5, 95.2 (s, 4-C, 5-C, 8-C and 9-C), 121.6, 122.8 (d, 6-C and 7-C), 126.0, (d, 19-C) 126.4 (d, 18-C), 126.6 (d, 14-C), 129.8 (d, 15-C), 131.1, 132.2 (s, 16-C and 20-C),133.5 (d, 17-C), 133.6 (d, 13-C), 135.3 (s, 12-C), 143.8 (s, 1-C); *m/z* (LREI) 308 (M^+; 15%), 243 (37), 190 (100), 165 (18), 133 (16), 70 (16); *m/z* (HREI) calcd for $C_{18}H_{12}S_2O$ 308.0330; found 308.0336.

1,8-Dibromooct-4-ene-2,6-diyne (78).[72]



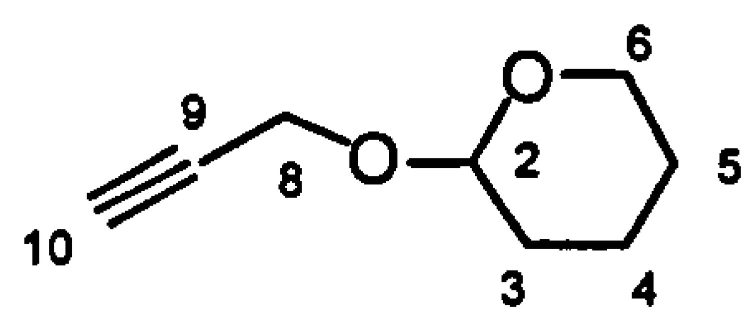
To a mixture of PPh_3 (11 g, 42.0 mmol) and bromine (2 cm^3, 38.9 mmol) in dichloromethane (50 cm^3) under nitrogen atmosphere, 1,8-bis(tetrahydropyran-2'-yloxy)oct-4-ene-2,6-diyne (3.39 g, 11.1 mmol) was added dropwise at 0 °C over 2 hours. After the addition the flask was allowed to reach room temperature and the mixture was stirred for a further 2.5 hours. The majority of the solvent was removed *in vacuo*. The remainder of the solution was poured into a beaker containing petroleum ether (20 cm^3). The black precipitate was filtered, washed with petroleum ether (3 x 30 cm^3), and the combined organic layers were concentrated *in vacuo*. Purification by column chromatography (60-80 petroleum ether) gave **78** (2.44 mg, 83%) as a light yellow oil; R_f 0.4 (60-80 petroleum ether); υ_{max} (nujol)/cm^{-1} 1687 (C=C), 2215 (C≡C); δ_H(360 MHz; $CDCl_3$) 4.14 (2H, s, 4-H and 5-H), 5.91 (4H, s, 1-H and 8-H); δ_C (90 MHz; $CDCl_3$) 14.9 (t, 1-C and 8-C), 83.5 (s, 3-C and 6-C), 92.3 (s, 2-C and 7-C), 120.2 (d, 4-C and 5-C); *m/z* (LREI) 264 (M^+; 15%), 262 (30), 260 (17), 183 (96), 181 (100), 102 (95).

1,8-Bis(tetrahydropyran-2'-yloxy)oct-4-ene-2,6-diyne (80).[72]



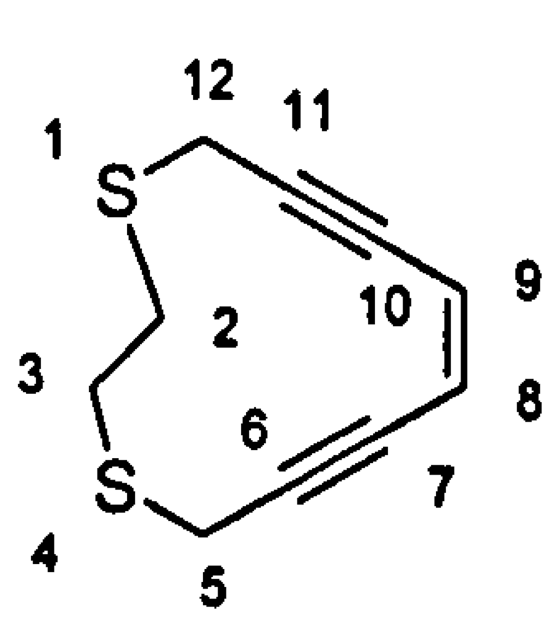
A mixture of 2-propargyloxytetrahydropyran (11.1 g, 80 mmol), palladium(0) tetrakis(triphenylphosphine) (1 g, 0.86 mmol), copper(I) iodide (1 g, 5.25 mmol) and butylamine (25 cm^3, 250 mmol) was dissolved in 150 cm^3 of dry benzene in a two-neck flask under nitrogen atmosphere, and cooled to 0 °C. (*Z*)-1,2-Dichloroethene (3 cm^3, 40 mmol) was then added dropwise. Upon completion of the addition, the mixture was allowed to reach room temperature and stirred overnight (16h). The solvent was removed *in vacuo* and the residue was chromatographed (60-80 petroleum ether:diethyl ether 80:20) on silica gel to afford **80** (10.00 g, 82%) as a yellow oil, R_f 0.24 (60-80 petroleum ether:diethyl ether 80:20); υ_{max} (nujol)/cm^{-1} 1690 (C=C), 2216 (C≡C); δ_H(360 MHz; $CDCl_3$) 1.55 (8H, m, 2-H, 3-H, 16-H and 17-H), 1.75 (4H, m, 4-H and 15-H), 3.49 (2H, m, 1-H_a and 18H_a), 3.78 (2H, m, 1-H_b and 18H_b), 4.39 (4H, d, *J* 4.3 Hz, 6-H and 13-H), 4.81 (2H, t, *J* 3.4 Hz, 5-H and 14-H), 5.79 (2H, s, 9-H and 10-H); δ_C(90 MHz, $CDCl_3$) 19.2 (t, 6-C and 13-C), 25.5 (t, 3-C and 16-C), 30.4 (t, 2-C and 17-C), 54.8 (t, 4-C and 15-C), 62.2 (t, 1-C and 18-C), 83.2 (s, 8-C and 11-C), 93.1 (s, 7-C and 12-C), 96.8 (d, 5-C and 14-C), 119.6 (d, 9-C and 10-C); *m/z* (LREI) 304 (M^+; 0.3%), 220 (6), 136 (25), 85 (100), 55 (54).

2-Propargyloxytetrahydropyran (82).[75]



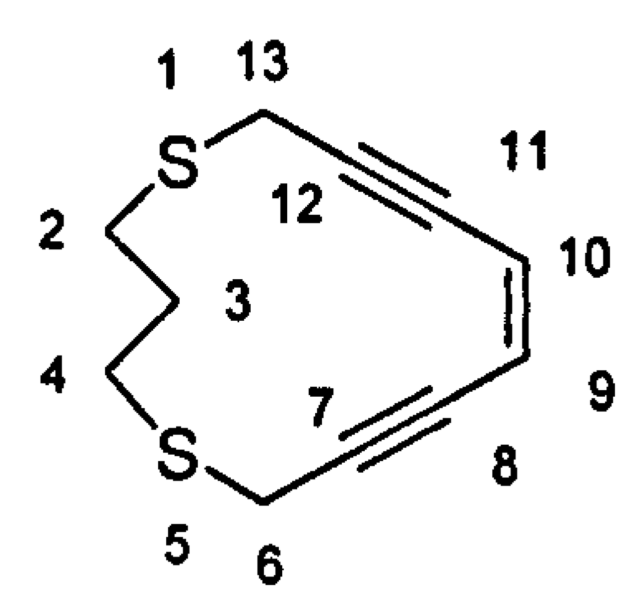
(±)-Camphorsulfonic acid (0.116 g, 0.5 mmol), dichloromethane (750 cm^3) and propargyl alcohol (29.4 cm^3, 0.5 mol) were charged sequentially in an oven-dried, 2-L, three-neck flask equipped with a magnetic stirring bar, a rubber septum, a nitrogen inlet adapter and an oven-dried, 200 cm^3 pressure-equalising addition funnel sealed with a rubber septum. The flask was cooled to 0 °C and a solution of 3,4-dihydro-2H-pyran (50.2 cm^3, 0.550 mol) in dichloromethane (75 cm^3) was added dropwise over 2h. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to reach room temperature. After 2h at room temperature, the reaction mixture was transferred to a separatory funnel and extracted with saturated sodium bicarbonate solution (100 cm^3). The organic phase was separated and washed with saturated sodium chloride solution (100 cm^3), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by distillation through a Vigreux column first at atmospheric pressure (to remove traces of solvent) and then at reduced pressure (3 mmHg, 44 °C), to afford **82** (58.18 g, 83%) as a colourless liquid; υ_{max} (nujol)/cm^{-1} 1121/1202 (C-O), 2118 (C≡C); δ_H(360 MHz; $CDCl_3$) 1.51-1.87 (6H, m, 3,4,5-H), 2.41 (1H, t, *J* 2.4 Hz, 10-H), 3.55-3.57 (1H, m, 6-H_a), 3.81-3.87 (1H, m, 6-H_b), 4.23 (2H, dd, *J* 15.6 and 2.4 Hz, 8-H), 4.30 (1H, dd, *J* 15.6 and 2.3 Hz, 2-H); δ_C(90 MHz, $CDCl_3$) 19.0 (t, 8-C), 25.3 (t, 4-C), 30.2 (t, 5-C), 54.0 (t, 3-C), 61.9 (t, 6-C), 74.0 (d, 10-C) 79.8 (s, 9-C) 96.7 (d, 2-C); *m/z* (LREI) 140 (M^+; 1 %), 139 (12), 101 (7), 85 (100), 56 (62).

1,4 Dithia-cyclododec-8-ene-6,10-diyne (93).



Potassium hydroxide (110 mg, 1.96 mmol) was dissolved in methanol (150 cm^3). A mixture of 1,8-dibromooct-4-ene-2,6-diyne (254 mg, 0.98 mol) and 1,2-ethanedithiol (0.123 cm^3, 1.47 mol) in THF/methanol (9:1, 100 cm^3) was added dropwise over 1h. After the end of the addition the mixture was stirred for a further 1.5 hours. The solvent was removed under reduced pressure. The residue was diluted with dichloromethane (50 cm^3) and washed with brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexane) gave **93** (135 mg, 78%) as a yellow crystalline solid, R_f 0.60 (80:20 60-80 petroleum ether:diethyl ether); υ_{max} (neat)/cm^{-1} 1577 (C=C), 2222 (C≡C); mp 27-28 °C (dichloromethane); δ_H(400 MHz; $CDCl_3$) 3.01 (4H, s, 2-H and 3-H), 3.48 (4H, d, *J* 0.6 Hz , 5-H and 12-H), 5.80 (2H, t, *J* 0.6 Hz, 8-H and 9-H); δ_C(100 MHz, $CDCl_3$) 20.8 (t, 5-C and 12-C), 31.9 (t, 2-C and 3-C), 83.0 (s, 7-C and 10-C), 92.9 (s, 6-C and 11-C), 121.5 (d, 8-C and 9-C); *m/z* (HREI) calcd for $C_{10}H_{10}S_2$ 194.0224; found 194.0224.

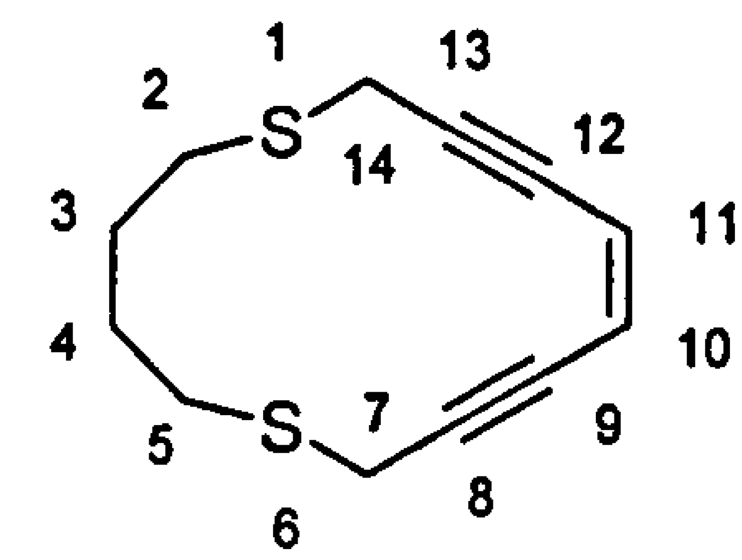
1,5-Dithia-cyclotridec-9-ene-7,11-diyne (94).



Potassium hydroxide (110 mg, 1.96 mmol) was dissolved in IMS (150 cm^3). A mixture of 1,8-dibromooct-4-ene-2,6-diyne (254 mg, 0.98 mol) and propane-1,2-dithiol (209 mg, 1.47 mol) in IMS/THF (9:1, 100 cm^3) was added dropwise over 1h. After the end of the addition the mixture was stirred for a further 1 hour. The solvent was removed under reduced pressure. The residue was diluted with dichloromethane (50 cm^3) and washed with brine. The organic layer was separated and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexane:diethyl ether 85:15) gave **94** (110 mg, 54%) as a white crystalline solid, R_f 0.33 (85:15 60-80 petroleum ether:diethyl ether); υ_{max} (nujol)/cm^{-1} 1694 (C=C), 2199 (C≡C); δ_H(360 MHz; $CDCl_3$) 2.24-2.33 (2H, m, 3-H), 2.80-2.85 (4H, m, 2-H and 4-H), 3.50 (4H, d, *J* 0.7 Hz, 6-H and 13-H), 5.83 (2H, t, *J* 0.7 Hz, 9-H and 10-H); δ_C(90 MHz, $CDCl_3$) 21.2 (t, 6-C and 13-C), 31.2 (t, 3-C), 32.5 (t, 2-C and 4-

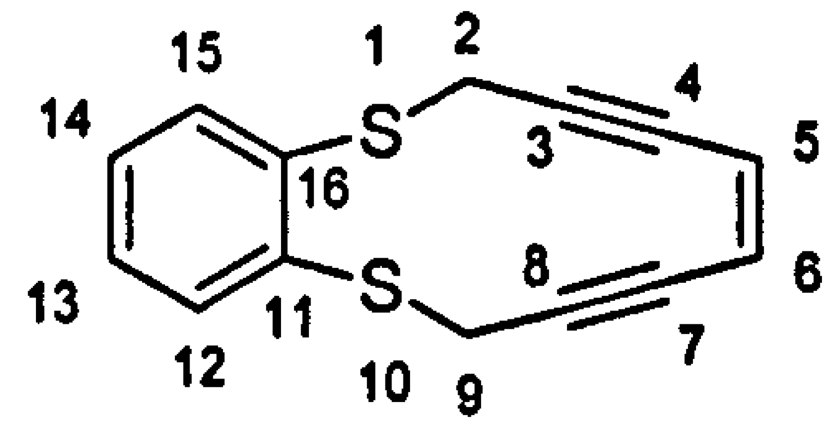
C), 81.2 (s, 8-C and 11-C), 93.7 (s, 7-C and 12-C), 120.1 (d, 9-C and 10-C); *m/z* (LREI) 208 (M^+; 44%), 134 (55), 106 (100), 102 (65), 76 (23).

1,6 Dithia-cyclotetradec-10-ene-8,12-diyne (95).



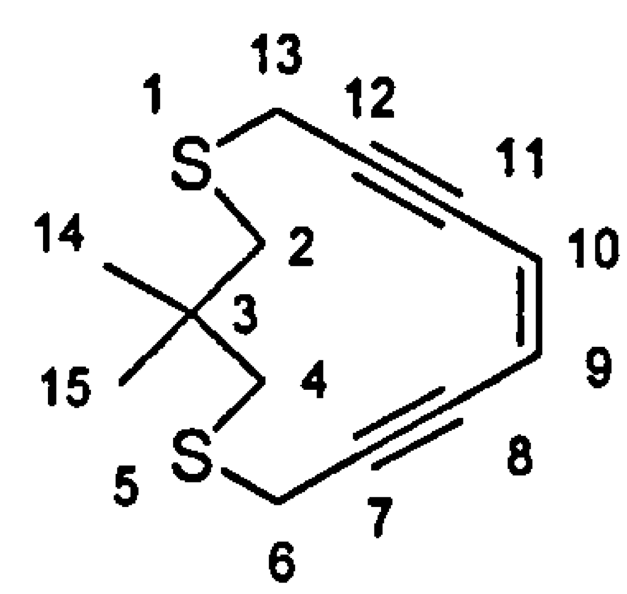
Potassium hydroxide (110 mg, 1.96 mmol) was dissolved in methanol (150 cm^3). A mixture of 1,8-dibromooct-4-ene-2,6-diyne (254 mg, 0.98 mol) and 1,3-butanedithiol (0.073 cm^3, 1.5 mol) in THF/methanol (9:1, 100 cm^3) was added dropwise over 2h. After the end of the addition the mixture was stirred for a further 30 minutes. The solvent was removed under reduced pressure. The residue was diluted with dichloromethane (50 cm^3) and washed with brine. The organic layer was separated and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (60-80 petroleum ether:diethyl ether 90:10) gave **95** (160 mg, 73%) as a colourless oil. R_f 0.48 (60-80 petroleum ether:diethyl ether); υ_{max} (neat)/cm^{-1} 1683 (C=C), 2084 (C≡C); δ_H(400 MHz; $CDCl_3$) 1.75-1.1.79 (4H, m, 3-H and 4-H), 2.76-2.79 (4H, m, 2-H and 5-H), 3.42 (4H, s, 7-H and 14-H), 5.76 (2H, s, 10-H and 11-H); δ_C(100 MHz, $CDCl_3$) 20.7 (t, 7-C and 14-C), 27.3 (t, 3-C and 4-C), 30.2 (t, 2-C and 5-C), 81.2 (s, 9-C and 12-C), 93.8 (s, 8-C and 13-C), 120.1 (d, 10-C and 11-C); *m/z* (HREI) calcd for $C_{12}H_{14}S_2$ 222.05369; found 222.05339.

1,10-Dithia-3,7-diyn-5-en-benzocyclododecene (96).



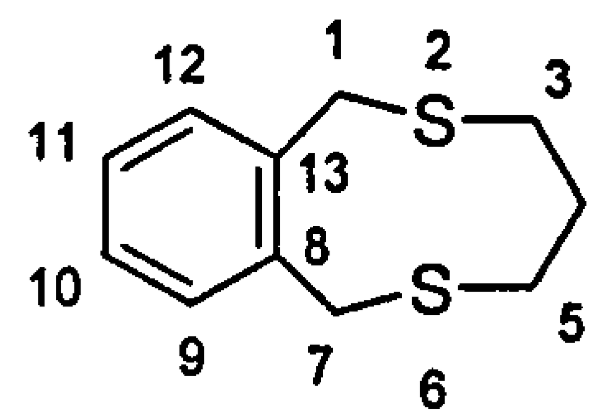
Potassium hydroxide (110 mg, 1.96 mmol) was dissolved in methanol (150 cm^3). A mixture of 1,8-dibromooct-4-ene-2,6-diyne (254 mg, 0.98 mol) and benzene-1,2-dithiol (209 mg, 1.47 mol) in THF/methanol (9:1, 100 cm^3) was added dropwise over 1h. After the end of the addition the mixture was stirred for a further 2.5 hours. The solvent was removed under reduced pressure. The residue was diluted with dichloromethane (50 cm^3) and washed with brine. The organic layer was separated and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexane) gave **96** (138 mg, 58%) as a yellow crystalline solid, R_f 0.40 (80:20 60-80 petroleum ether:diethyl ether); υ_{max} (neat)/cm^{-1} 1605 (Ar), 1685 (C=C), 2193 (C≡C); mp 110-112 °C (dichloromethane); δ_H(400 MHz; $CDCl_3$) 3.82 (4H, s, 2-H and 9-H), 5.59 (2H, m, 5-H and 6-H), 7.19 (2H, dd, *J* 5.9 and 3.4 Hz, 13-H and 14-H), 7.48 (2H, dd, *J* 5.9 and 3.4 Hz, 12-H and 15-H); δ_C(100 MHz, $CDCl_3$) 26.3 (t, 2-C and 9-C), 81.4 (s, 4-C and 7-C), 93.3 (s, 3-C and 8-C), 120.5 (d, 5-C and 6-C), 128.4 (d, 13-C and 14-C), 133.1 (d, 12-C and 15-C), 138.3 (s, 11-C and 16-C); *m/z* (HREI) calcd for $C_{14}H_{10}S_2$ 242.02240; found 242.02268.

3,3-Dimethyl-1,5-dithia-cyclotridec-9-ene-7,11-diyne (97).



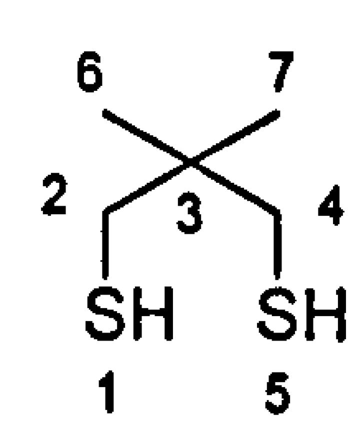
Potassium hydroxide (110 mg, 1.96 mmol) was dissolved in methanol (150 cm^3). A mixture of 1,8-dibromooct-4-ene-2,6-diyne (254 mg, 0.98 mol) and 2,2'-dimethyl-propane-1,3-dithiol (0.2 cm^3, 1.99 mol) in THF/methanol (9:1, 100 cm^3) was added dropwise over 1h. After the end of the addition the mixture was stirred for a further 1.5 hours. The solvent was removed under reduced pressure. The residue was diluted with dichloromethane (50 cm^3) and washed with brine. The organic layer was separated and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexane) gave **97** (210 mg, 91%) as a colourless oil, R_f 0.21 (60-80 petroleum ether); υ_{max} (neat)/cm^{-1} 1666 (C=C), 2082 (C≡C); δ_H(400 MHz; $CDCl_3$) 1.07 (6H, s, 14-H and 15-H), 2.95 (4H, m, 2-H and 4-H), 3.50 (4H, s, 6-H and 13-H), 5.83 (2H, s, 9-H and 10-H); δ_C(100 MHz, $CDCl_3$) 23.5 (t, 6-C and 13-C), 26.7 (q, 14-C and 15-C), 36.7 (s, 3-C), 46.7 (t, 2-C and 4-C), 82.1 (s, 8-C and 11-C), 94.4 (s, 7-C and 12-C), 120.5 (d, 9-C and 10-C); *m/z* (HREI) calcd for $C_{13}H_{16}S_2$ 236.0693; found 236.0692.

2,6-Dithia-[7]orthocyclophane (104).[85]



Cesium carbonate (360 g, 1.1 mmol) was dissolved in DMF (60 cm^3) and the solution was heated to 55 °C. Addition of *o*-xylylene dibromide (291 mg, 1.1 mol) and 1,3-propanedithiol (0.11 cm^3, 1.1 mol) in DMF (20 cm^3) was started from a syringe pump. After the addition of the first 5 cm^3 over 6.5 hours, cesium carbonate (360 g, 1.1 mmol) was added in one portion. The second portion of the solution was then added over 6 hours. The flask was allowed to reach room temperature and the majority of the solvent was removed under reduced pressure. The residue was diluted with dichloromethane (50 cm^3) and washed with brine. The organic layer was separated and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (60-80 petroleum ether) gave **104** (100 mg, 43%) as a white crystalline solid; R_f 0.66 (80:20 60-80 petroleum ether:diethyl ether); mp 77-78 °C (60-80 petroleum ether); δ_H(400 MHz; $CDCl_3$) 1.81-1.87 (2H, m, 4-H), 2.56-2.59 (4H, m, 3-H and 5-H), 3.77 (4H, s, 1-H and 7-H), 7.23-7.29 (4H, m, 9-H, 10-H, 11-H and 12-H); δ_C(100 MHz, $CDCl_3$) 29.2 (t, 1-C and 7-C), 34.8 (t, 4-C), 35.6 (t, 3-C and 5-C), 128.26 (d, 10-C and 11-C), 130.5 (d, 9-C and 12-C), 138.8 (s, 8-C and 13-C); *m/z* (HREI) calcd for $C_{11}H_{14}S_2$ 210.05369; found 210.05349.

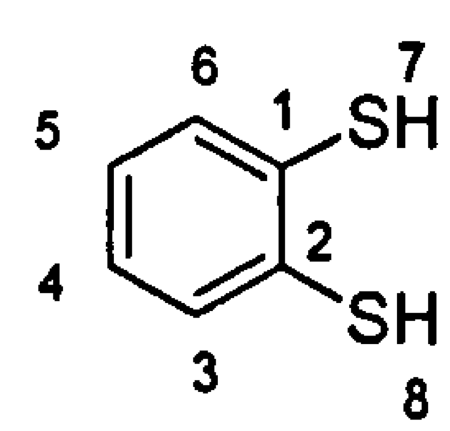
2,2-Dimethyl-propane-1,3-dithiol (108).[87]



Methanesulphonyl chloride (11.0 g, 96.2 mmol) and pyridine (25 cm^3) were mixed in a round-bottom flask and cooled to 0 °C. A solution of 2,2-dimethyl-propane-1,3-diol (5.0 g, 48.1 mmol) in pyridine (15 cm^3) was added dropwise over 5 minutes. The mixture was allowed to reach room temperature and stirred overnight (14h). The reaction was poured into a mixture of water, ice and conc. HCl, extracted with dichloromethane (3 x 50 cm^3) and washed with 1M HCl and brine. The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure to yield an orange solid. The solid was dissolved in DMF (50 cm^3) and to it was added two single portions of Na_2S (5g, 64.2 mmol) and S_8 (0.6 g, 9.5 mmol). The mixture was then heated at 100 °C for 3 days, cooled to room temperature and poured into a beaker containing water and ice. The organic portion was extracted with diethyl ether (3x50 cm^3). The aqueous layer was acidified with concentrated HCl and extracted once more with diethyl ether (50 cm^3). The combined ethereal portions were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to yield dark yellow oil (5.5 g).

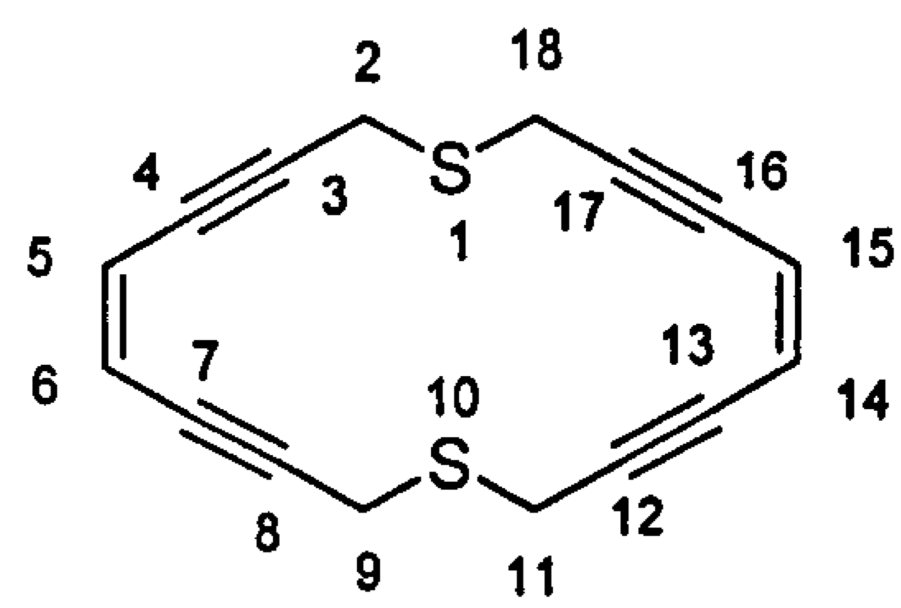
The oil was dissolved in diethyl ether (50 cm^3) and added dropwise to a slurry of $LiAlH_4$ (0.7g, 18.4 mmol) in diethyl ether (30 cm^3). The stirring was continued at room temperature for 4.5 h. The reaction was quenched with water first and then 10% H_2SO_4, extracted with diethyl ether (3x30 cm^3), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by Kugelröhr distillation (10 mmHg, 150 °C) gave **108** (2.55 g, 39%) as pale yellow oil; δ_H(400 MHz; $CDCl_3$) 0.98 (6H, s, 6-H and 7-H), 1.19 (2H, t, *J* 8.8 Hz, 1-H and 5-H), 2.53 (4H, d, *J* 8.8 Hz, 2-H and 4-H); δ_C(100 MHz, $CDCl_3$) 22.7 (s, 6-C and 7-C), 35.1 (s, 3-C), 35.7 (s, 2-C and 4-C); *m/z* (LREI) 136 (M^+; 22 %), 112 (14), 97 (17), 69 (50), 55 (100).

Benzene-1,2-dithiol (111).[88]



A mixture of TMEDA (1.6 cm^3, 11.0 mmol) and *n*-BuLi (2 M in Hexane, 12 cm^3, 24.0 mmol) in hexane (15 cm^3) was cooled to naught degrees. Thiophenol (1 cm^3, 10.0 mmol) was added dropwise *via* syringe. After stirring for 1h at 0 °C, the flask was allowed to reach room temperature and the mixture was stirred overnight (16h). The resulting white cloudy mixture was cooled to –20 °C and S_8 (320 mg, 10.0 mmol) was intorduced in one portion. The reaction was stirred for 60h, quenched with 10% HCl, extracted with diethyl ether (5x50 cm^3), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexane) gave **111** (1.07 g, 75%) as a yellow oil, R_f 0.30 (80:20 60-80 petroleum ether:diethyl ether); δ_H(400 MHz; $CDCl_3$) 3.78 (2H, s, 7-H and 8-H), 7.12 (2H, dd, *J* 5.8 and 3.4 Hz, 4-H and 5-H), 7.41 (2H, dd, *J* 5.8 and 3.4 Hz, 3-H and 6-H); δ_C(100 MHz, $CDCl_3$) 127.2 (d, 4-C and 5-C), 131.5 (d, 3-C and 6-C), 131.6 (s, 1-C and 2-C); *m/z* (HREI) calcd for $C_6H_6S_2$ 141.99019; found 141.99084.

1,10-Dithia-cyclooctadeca-5,14-diene-3,7,12,16-tetrayne (112).



Na_2S (12 g, 50 mmol) was dissolved in water (40 cm^3) in a 250 cm^3 round-bottom flask. Al_2O_3 (8.6 g) was added in one portion and the mixture stirred for 30 minutes. The water was then removed *in vacuo*, keeping the temperature of the bath below 65 °C. The resulting powder was then dried under vacuum pump (4 mmHg, 130 °C) for 1 hour. The titre of the resulting Na_2S impregnated on alumina is about 35% w/w.

Na_2S/Al_2O_3 (578 mg, 15.2 mmol) was dispersed in ethanol/dichloromethane (2:5, 160 cm^3) and the mixture was cooled down to zero degrees. 1,8-Dibromooct-4-ene-2,6-diyne (1.00 g, 3.80 mmol) was dissolved in the same solvent mixture (40 cm^3) and was added dropwise over 2h at naught degrees. After the end of the addition the mixture was stirred for a further 10 minutes. The mixture was filtered through celite and the filtrate washed with brine. After separation, the organic solvent was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (96:4 60-80 petroleum ether:diethyl ether) gave **112** (230 mg, 45%) as a white crystalline solid, R_f 0.56 (80:20 60-80 petroleum ether:diethyl ether); υ_{max} (nujol)/cm^{-1} 2360 (C≡C); mp 40-41 °C (80:20 60-80 petroleum ether:diethyl ether); δ_H(360 MHz; $CDCl_3$) 3.74 (8H, s, 2-H, 9-H, 11-H and 18-H), 5.88 (4H, s, 5-H, 6-H, 14-H and 15-H); δ_C(90 MHz, $CDCl_3$) 20.1 (t, 2-C, 9-C, 11-C and 18-C), 81.6 (s, 4-C, 7-C, 13-C and 16-C), 92.7 (s, 3-C, 8-C, 12-C and 17-C), 120.8 (d, 5-C, 6-C, 14-C and 15-C) *m/z* (LREI) 268 (M^+; 10%), 234 (100), 102 (20), 89 (20), 76 (14); *m/z* (HREI) calcd for $C_{16}H_{12}S_2$ 268.03804; found 268.03899.

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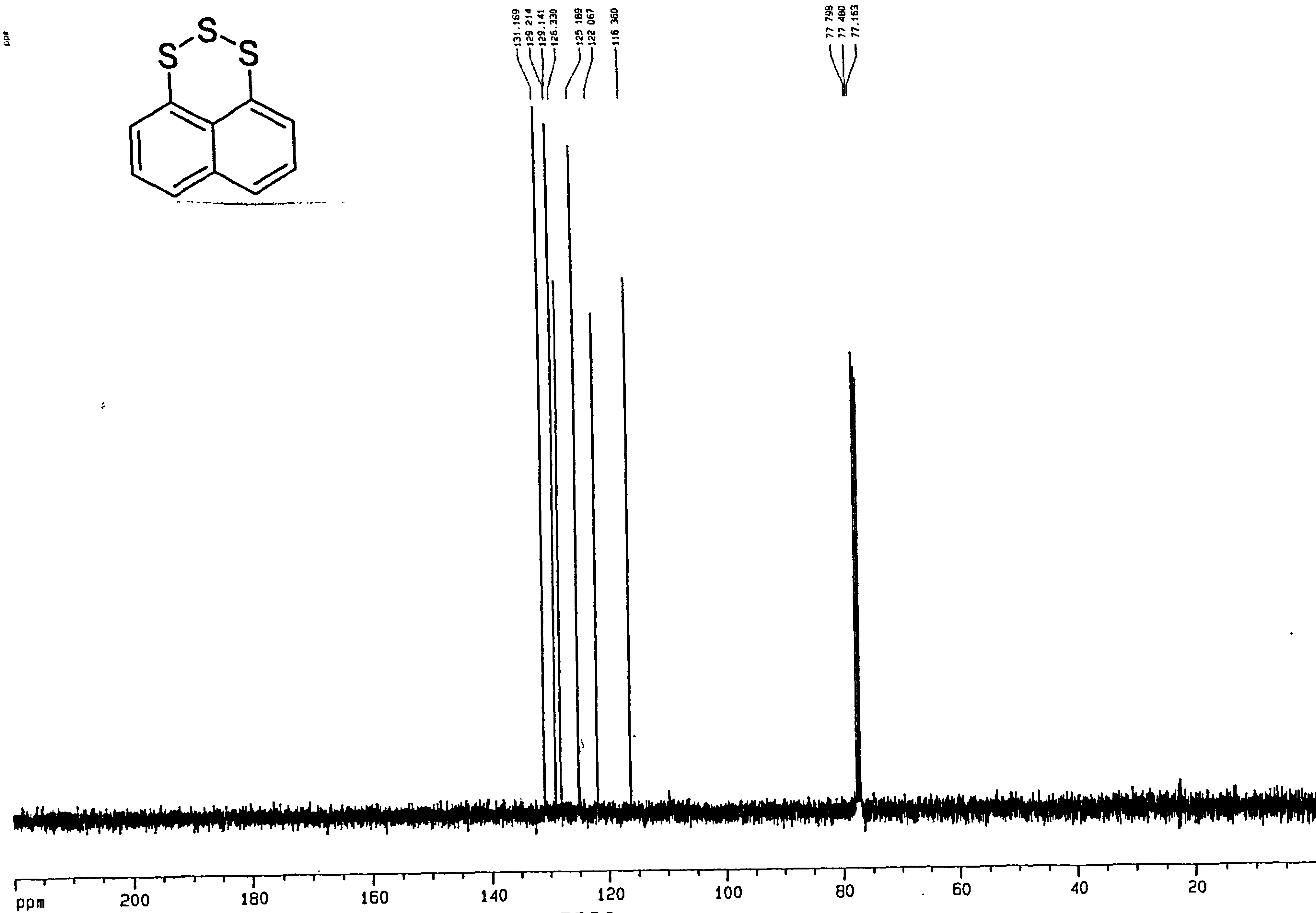

TRIS

C13CPDONLY_kcl CDCl3 {C:\u} General 10

Current Data Parameters

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PROCNO	1

F2 - Acquisition Parameters

Date_	20011107
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PROBHD	5 mm QNP 1H/1
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	30120.482 Hz
FIDRES	0.459602 Hz
AQ	1.0879476 sec
RG	1149.4
DW	16.600 usec
DE	6.00 usec
TE	300.0 K
D1	0.01000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

============ CHANNEL f1 =======

NUC1	13C
P1	9.00 usec
PL1	6.00 dB
SFO1	100.6237964 MHz

============ CHANNEL f2 =======

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	19.00 dB
PL13	19.00 dB
SFO2	400.1316005 MHz

F2 - Processing parameters

SI	32768
SF	100.6127290 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	23.00 cm
CY	12.50 cm
F1P	220.000 ppm
F1	22134.80 Hz
F2P	-1.000 ppm
F2	-100.61 Hz
PPMCM	9.60870 ppm/cm
HZCM	966.75708 Hz/cm


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TD 32768
SW 5494.505
HZ/PT .335
PW 3.0
RD 0.0
AQ 2.982
RG 40
NS 24
TE 297
O2 0.0
DP 63L PO
LB 0.0
GB 0.0
CX 40.00
CY 23.00
F1 9.000P
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PPM/CM .235
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O
PPM
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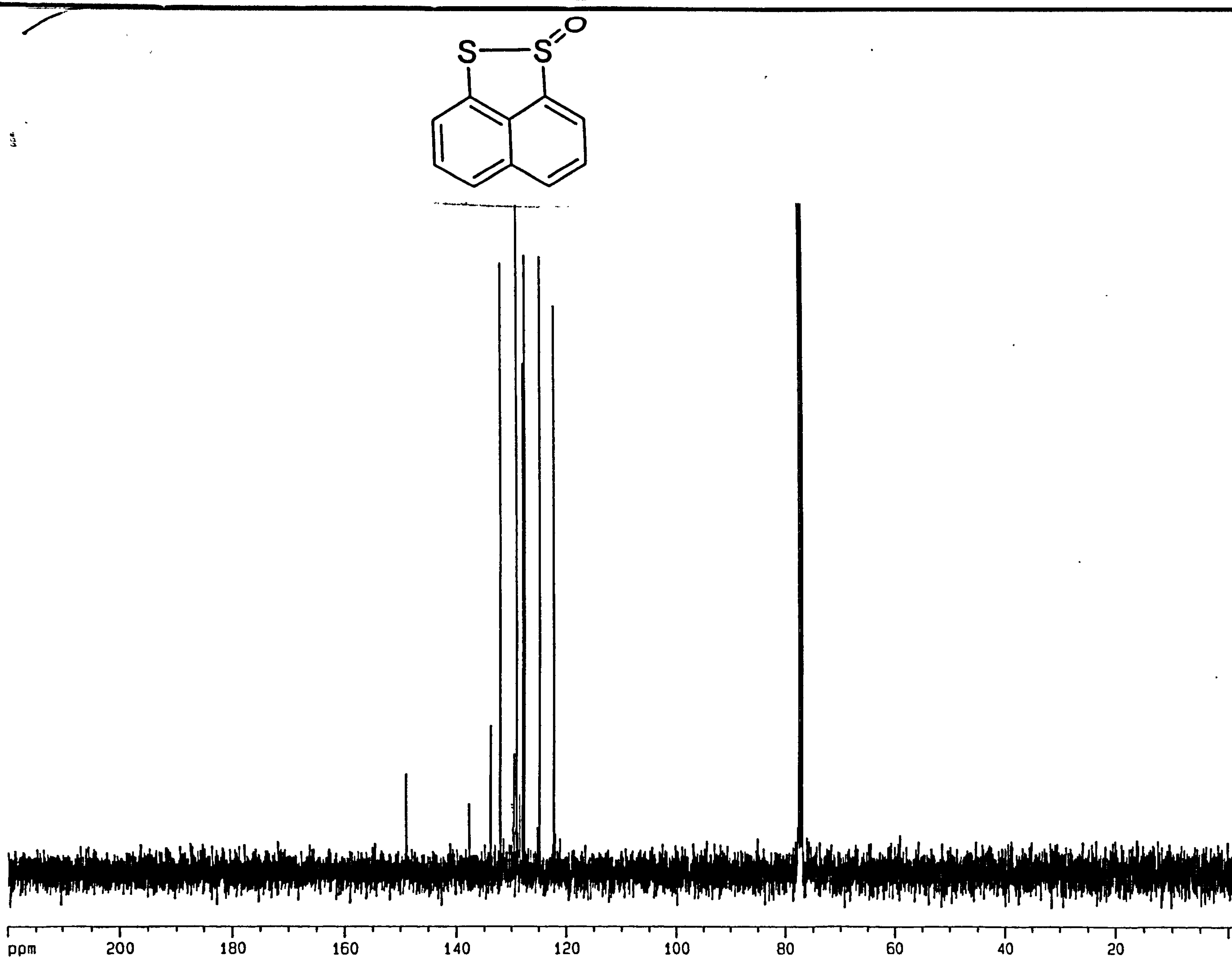

THIOS

C13CPDONLY_kc1 CDC13 {C: \u} General 9

Current Data Parameters

NAME	Nov06-2001-4-9
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20011106
Time	17.49
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zgpg30
TD	65536
SOLVENT	CDC13
NS	512
DS	4
SWH	30120.482 Hz
FIDRES	0.459602 Hz
AQ	1.0879476 sec
RG	2048
DW	16.600 usec
DE	6.00 usec
TE	300.0 K
D1	0.01000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

============ CHANNEL f1 =======

NUC1	13C
P1	9.00 usec
PL1	6.00 dB
SFO1	100.6237964 MHz

============ CHANNEL f2 =======

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	19.00 dB
PL13	19.00 dB
SFO2	400.1316005 MHz

F2 - Processing parameters

SI	32768
SF	100.6127290 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	23.00 cm
CY	12.50 cm
F1P	220.000 ppm
F1	22134.80 Hz
F2P	-1.000 ppm
F2	-100.61 Hz
PPMCM	9.60870 ppm/cm
HZCM	966.75708 Hz/cm

235.AP
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HZ/PT .328
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RD 0.0
AQ 3.047
RG 2
NS 24
TE 297
O2 0.0
DP 63L PO
LB 0.0
GB 0.0
CX 40.00
CY 23.00
F1 8.000P
F2 7.001P
HZ/CM 8.999
PPM/CM .025
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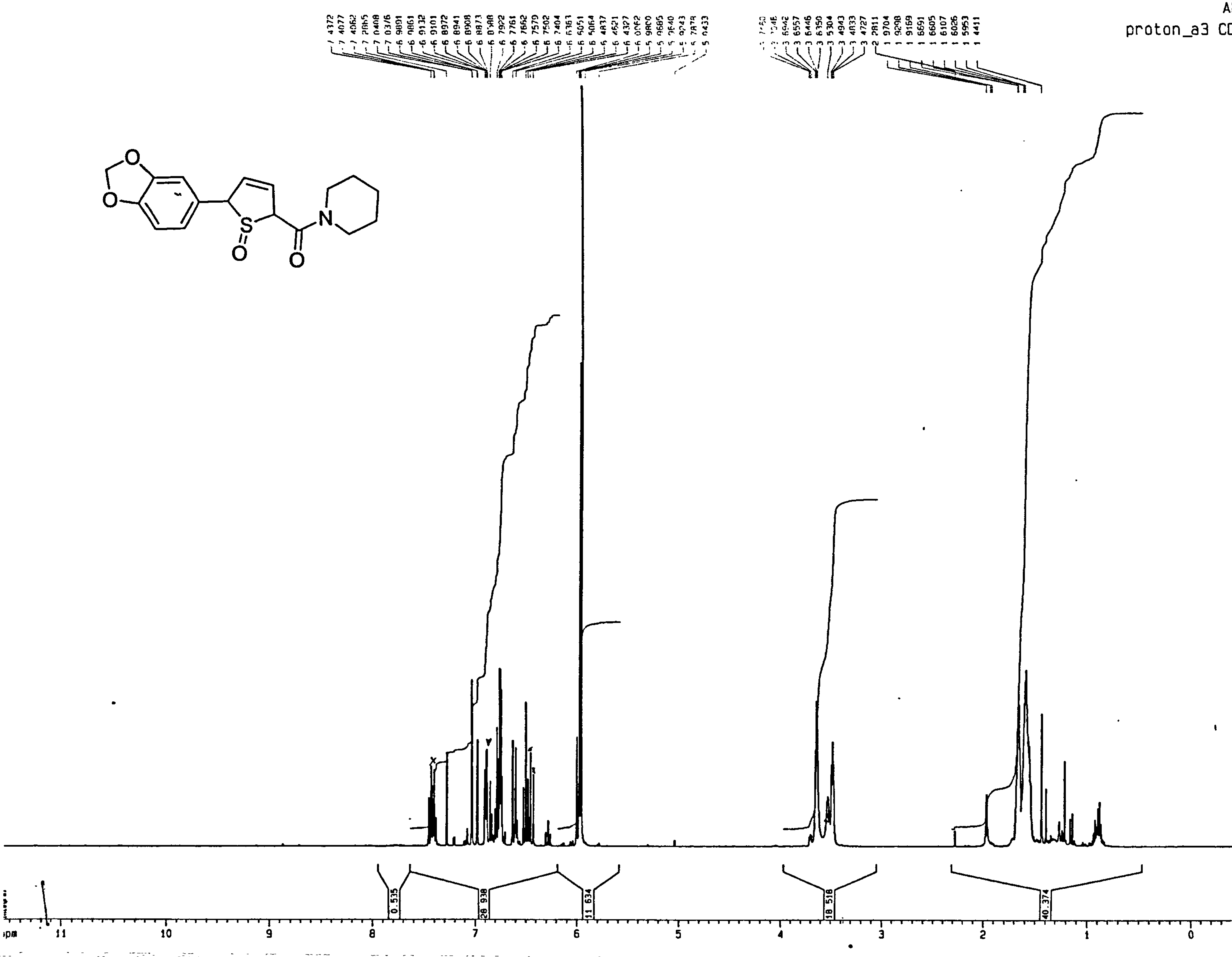
AP404B

proton_a3 CDCl3 C:/u jeh 42



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PROCNO 1

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INSTRUM drx500
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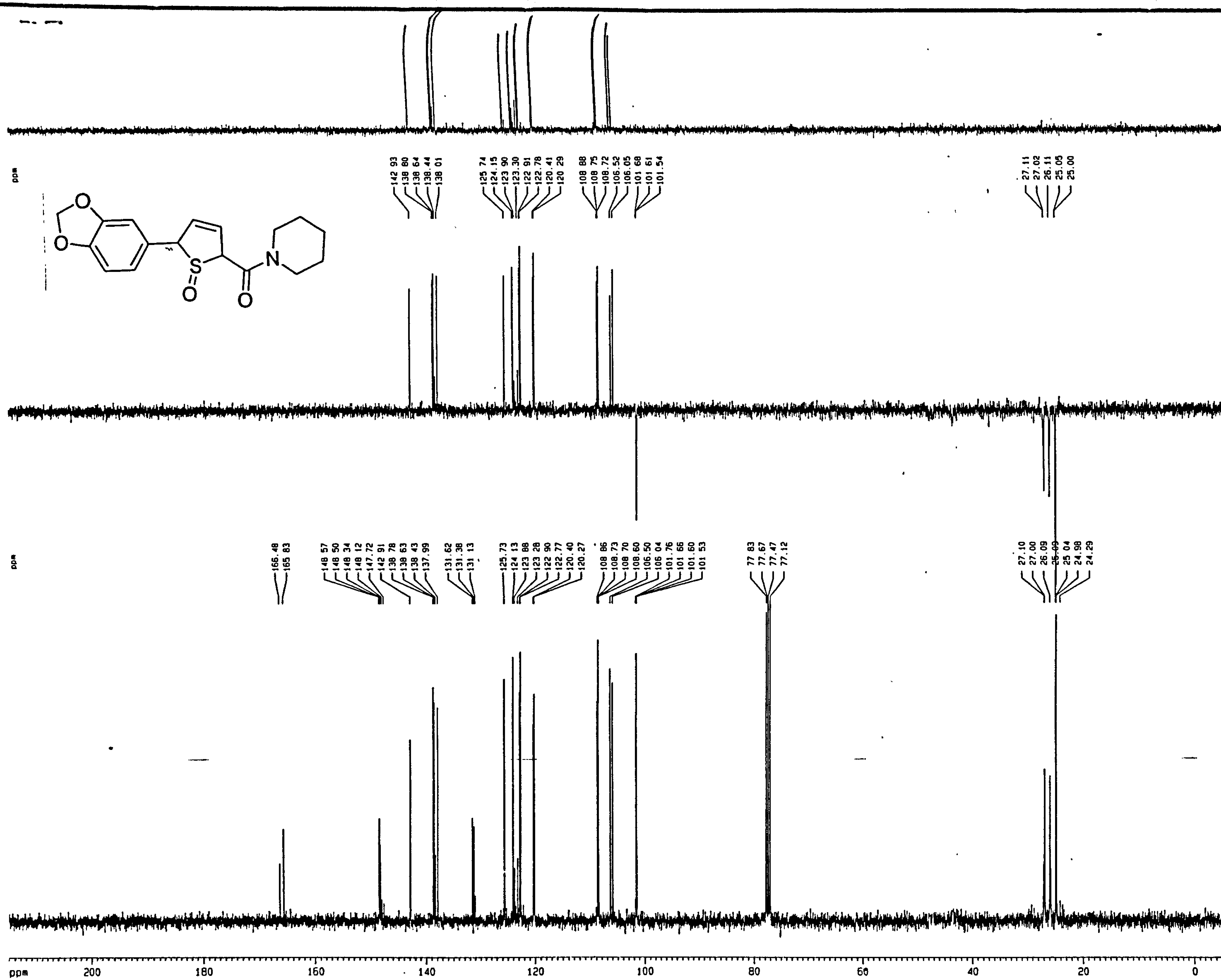
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 71.8
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

============ CHANNEL f1 ============
NUC1 1H
P1 11.75 usec
PL1 0.00 dB
SFO1 500.1330885 MHz

F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 5.00

1D NMR plot parameters
CX 35.00 cm
F1P 11.600 ppm
F1 5801.51 Hz
F2P -0.400 ppm
F2 -200.05 Hz
PPMCM 0.34286 ppm/cm
HZCM 171.47314 Hz/cm

c13cpdno.k CDCl3 {C:\bruker\xwin-nmr} ap 47



Current Data Parameters

NAME	ap-Aug06-2001
EXPNO	7
PROCNO	1

F2 - Acquisition Parameters

Date_	20010806
Time	23.25
INSTRUM	AV360
PROBHD	5 mm QNP 1H/1
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	640
DS	4
SWH	27173 912 Hz
FIDRES	0.414641 Hz
AQ	1.2059124 sec
RG	13004
DW	18 400 usec
DE	6 00 usec
TE	300.0 K
D1	0.01000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	5.88 usec
PL1	3.00 dB
SFO1	90.5646860 MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	87.00 usec
PL2	3.00 dB
PL12	22.00 dB
PL13	120.00 dB
SFO2	360.1314405 MHz

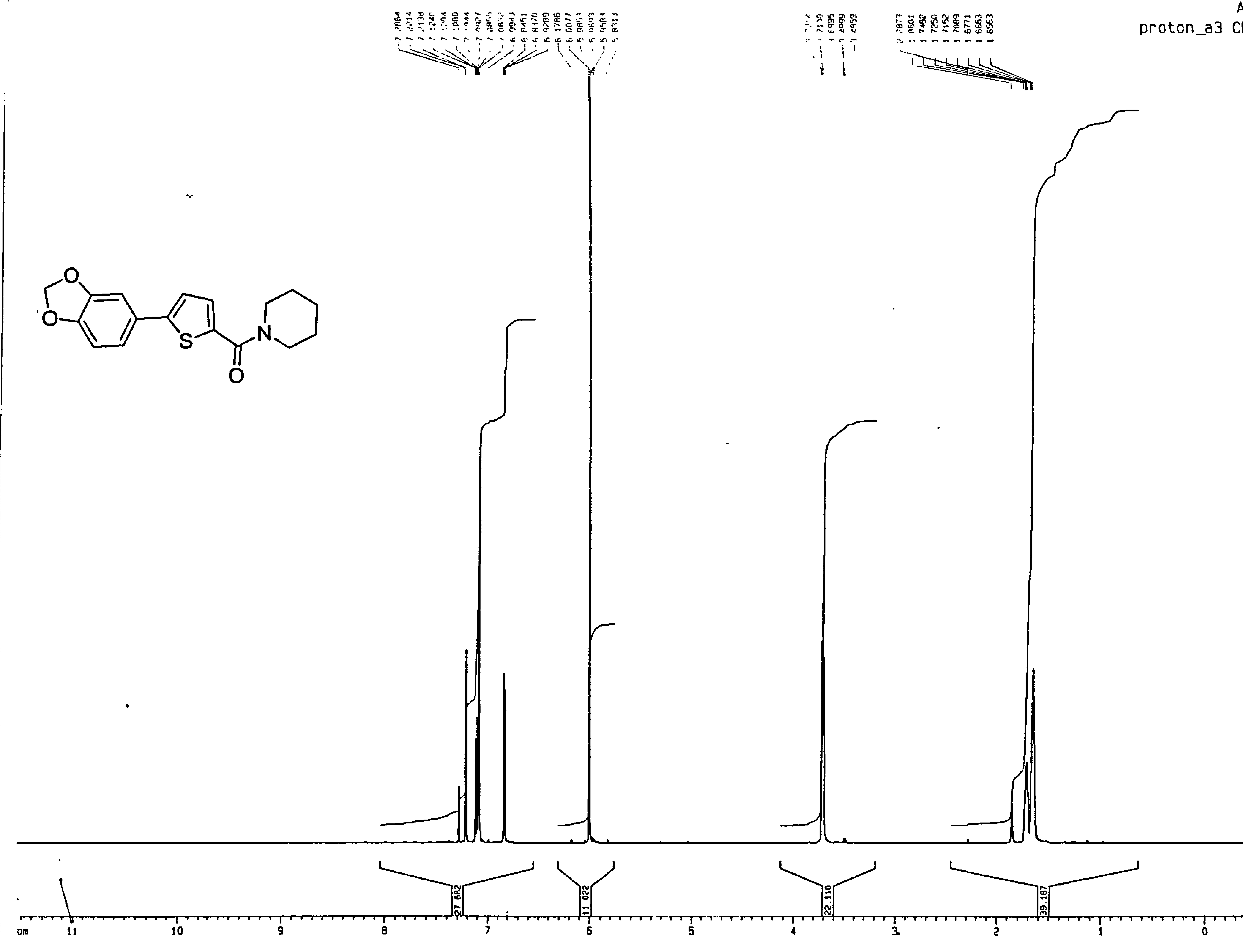
F2 - Processing parameters

SI	32768
SF	90.5547250 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1 40

1D NMR plot parameters

CX	35.00 cm
CY	8.70 cm
F1P	215.000 ppm
F1	19469.27 Hz
F2P	-5.000 ppm
F2	-452.77 Hz
PPMCM	6.28571 ppm/cm
HZCM	569.20111 Hz/cm

AP404A
proton_a3 CDCl3 C: /u jeh 41



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EXPNO 10
PROCNO 1

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Time 21.31
INSTRUM drx500
PROBHD 5 mm BBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 90.5
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

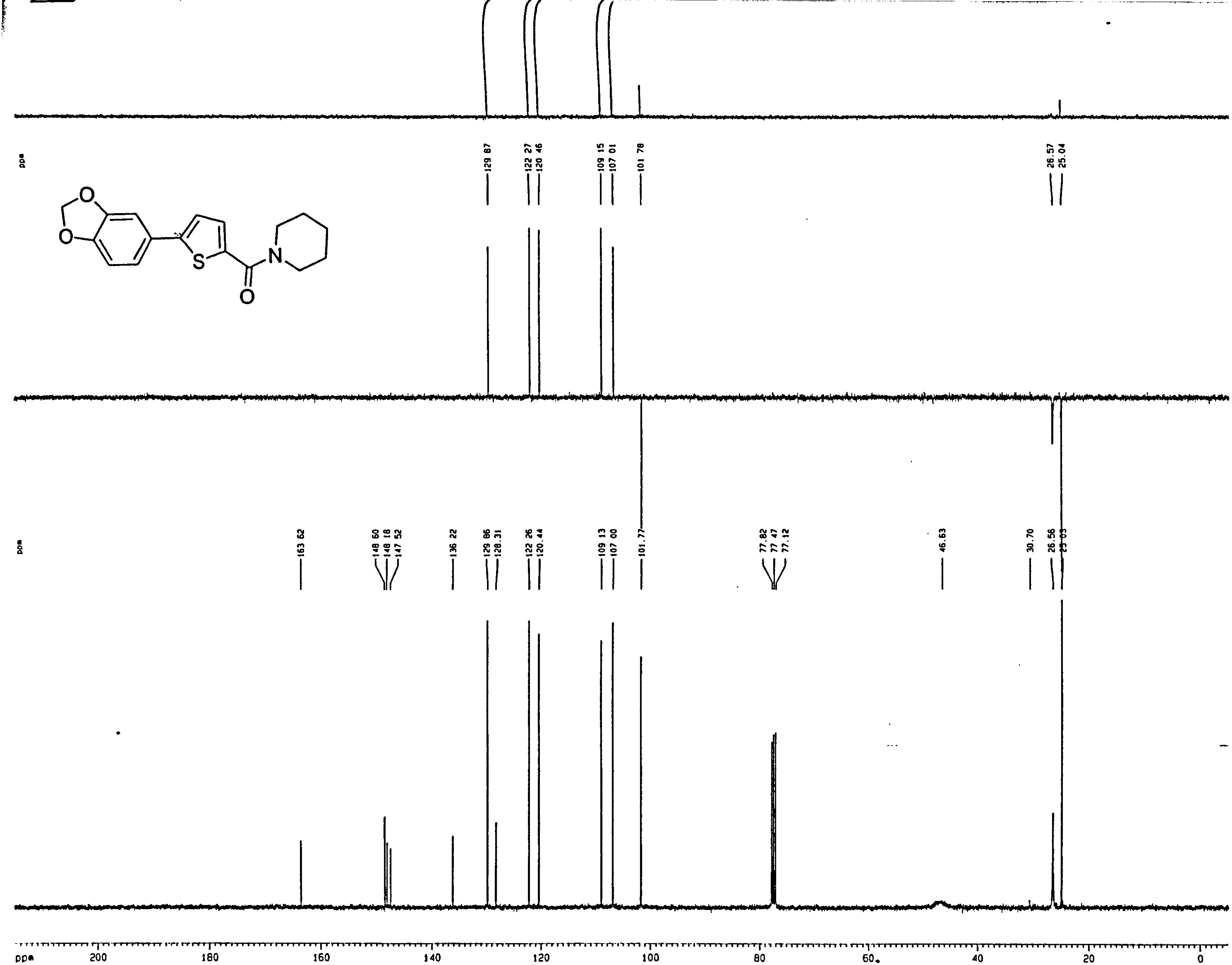
============ CHANNEL f1 ============
NUC1 1H
P1 11.75 usec
PL1 0.00 dB
SFO1 500.1330885 MHz

F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 5.00

1D NMR plot parameters
CX 35.00 cm
F1P 11.600 ppm
F1 5801.51 Hz
F2P -0.400 ppm
F2 -200.05 Hz
PPMCM 0.34286 ppm/cm
HZCM 171.47314 Hz/cm

ap404A

c13cpdno.k CDCl3 {C:\bruker\xwin-nmr} ap 46



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NAME ap-Aug06-2001
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 640
DS 4
SWH 27173.912 Hz
FIDRES 0.414641 Hz
AQ 1.2059124 sec
RG 2580.3
DW 18.400 usec
DE 6.00 usec
TE 300 0 K
D1 0 01000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

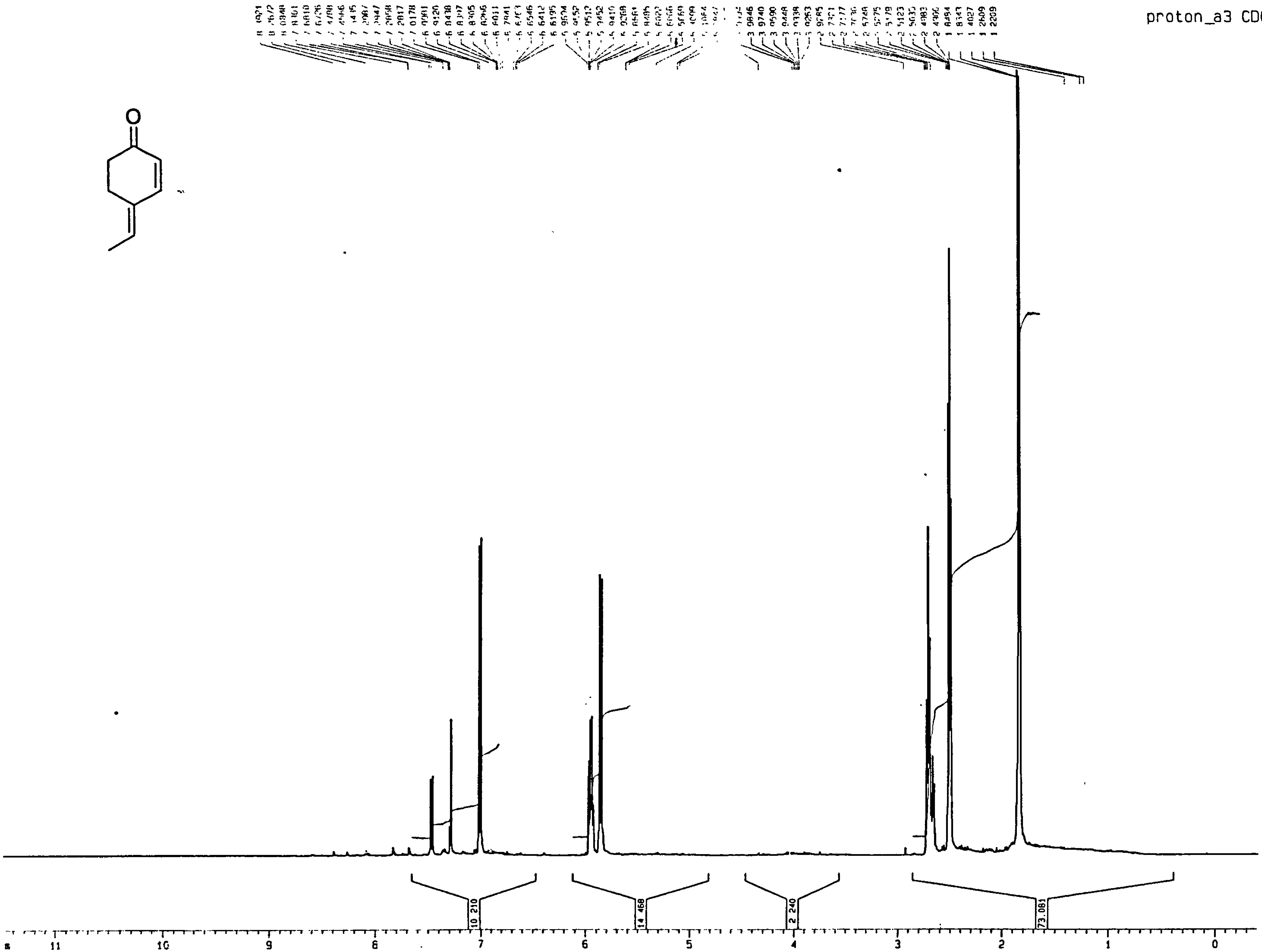
======== CHANNEL f1 ========
NUC1 13C
P1 5 88 usec
PL1 3.00 dB
SFO1 90 5646860 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 87.00 usec
PL2 3 00 dB
PL12 22.00 dB
PL13 120.00 dB
SFO2 360.1314405 MHz

F2 - Processing parameters
SI 32768
SF 90 5547250 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 35.00 cm
CY 8.70 cm
F1P 215.000 ppm
F1 19469 27 Hz
F2P -5 000 ppm
F2 -452.77 Hz
PPMCM 6.28571 ppm/cm
HZCM 569.20111 Hz/cm

proton_a3 CDCl3 C: /u jeh 17



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PROCNO 1

F2 - Acquisition Parameters
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Time 17.10
INSTRUM drx500
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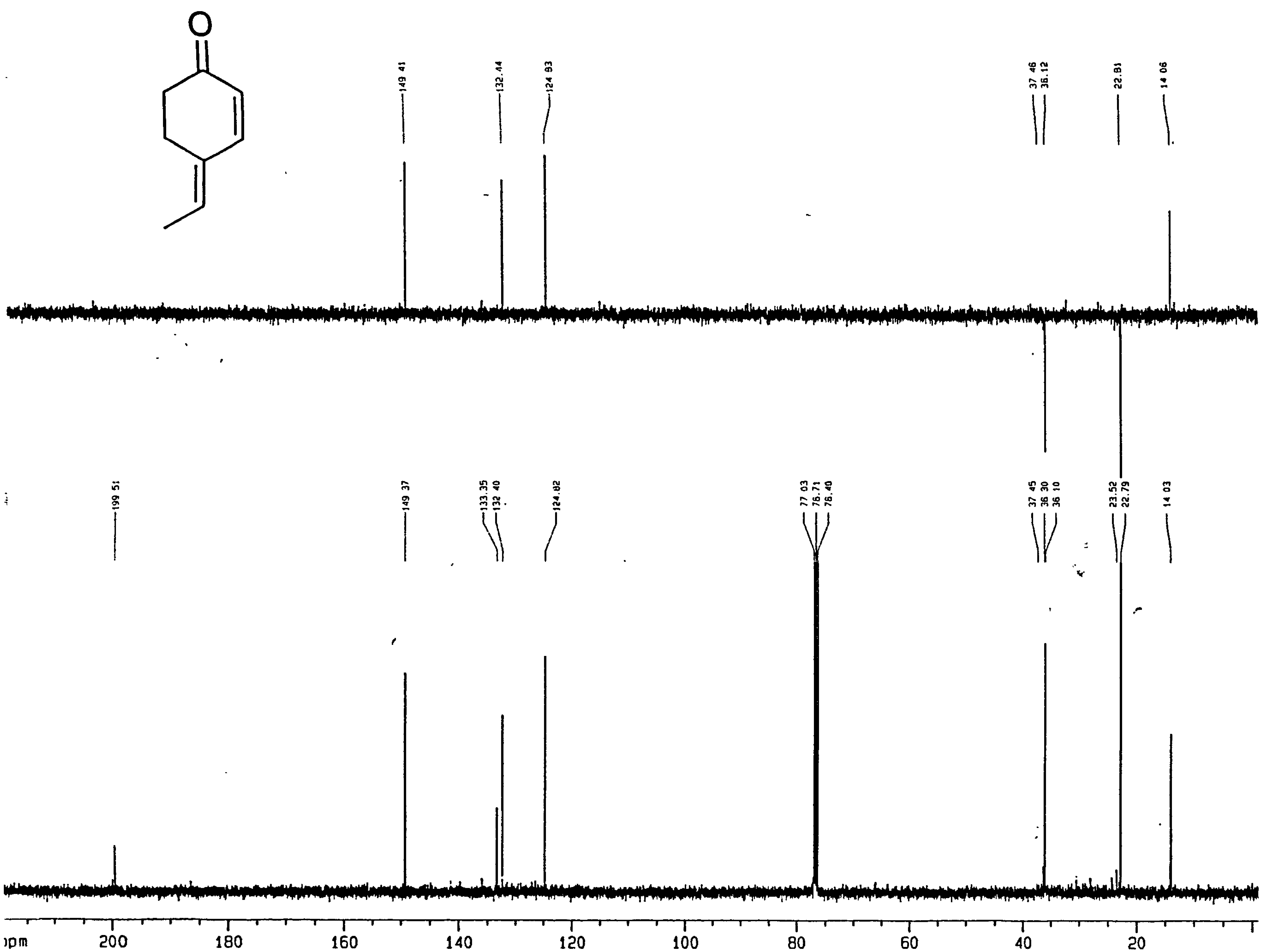
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 80.6
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

============ CHANNEL f1 ============
NUC1 1H
P1 11.75 usec
PL1 0.00 dB
SFO1 500.1330885 MHz

F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 5.00

1D NMR plot parameters
CX 35.00 cm
F1P 11.600 ppm
F1 5801.51 Hz
F2P -0.400 ppm
F2 -200.05 Hz
PPMCM 0.34266 ppm/cm
HZCM 171.47314 Hz/cm



AP390A

C13CPD_kcl CDCl3 {C:\u} General 1

Current Data Parameters

NAME	Oct29-2001-4-1
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20011029
Time	14.47
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	30120.482 Hz
FIDRES	0.459602 Hz
AQ	1.0879476 sec
RG	1625.5
DW	16.600 usec
DE	6.00 usec
TE	300.0 K
D1	0.01000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

============ CHANNEL f1 =======

NUC1	13C
P1	9.00 usec
PL1	6.00 dB
SFO1	100.6237964 MHz

============ CHANNEL f2 =======

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	18.00 dB
PL13	18.00 dB
SFO2	400.1316005 MHz

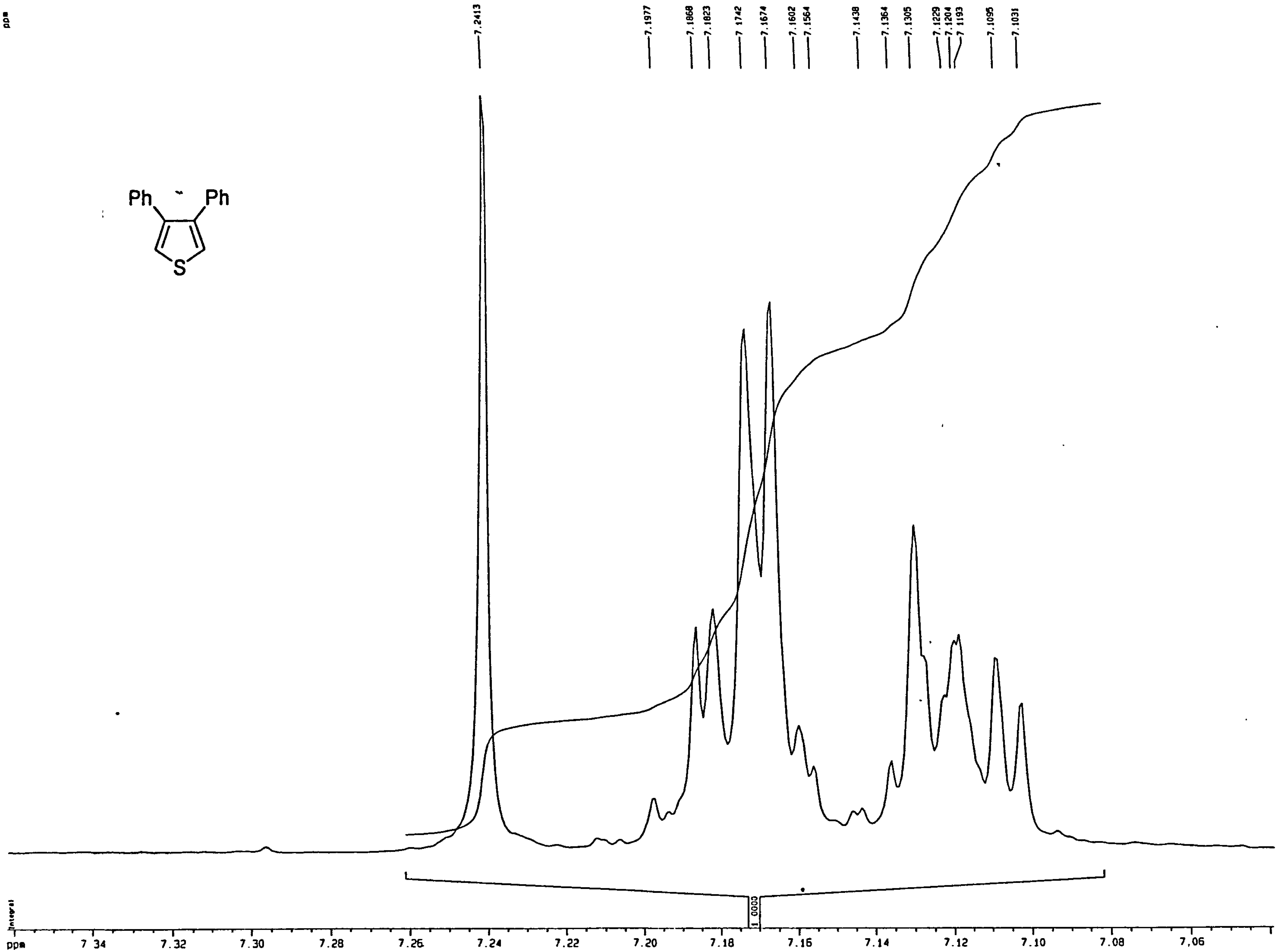
F2 - Processing parameters

SI	32768
SF	100.6128039 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	23.00 cm
CY	6.30 cm
F1P	220.000 ppm
F1	22134.82 Hz
F2P	-1.000 ppm
F2	-100.61 Hz
PPMCM	9.60870 ppm/cm
HZCM	966.75775 Hz/cm

proton.k CDCl3 {C:\bruker\xwin-nmr} ap 56



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NAME ap-Jun02-2001
EXPNO 1
PROCNO 1

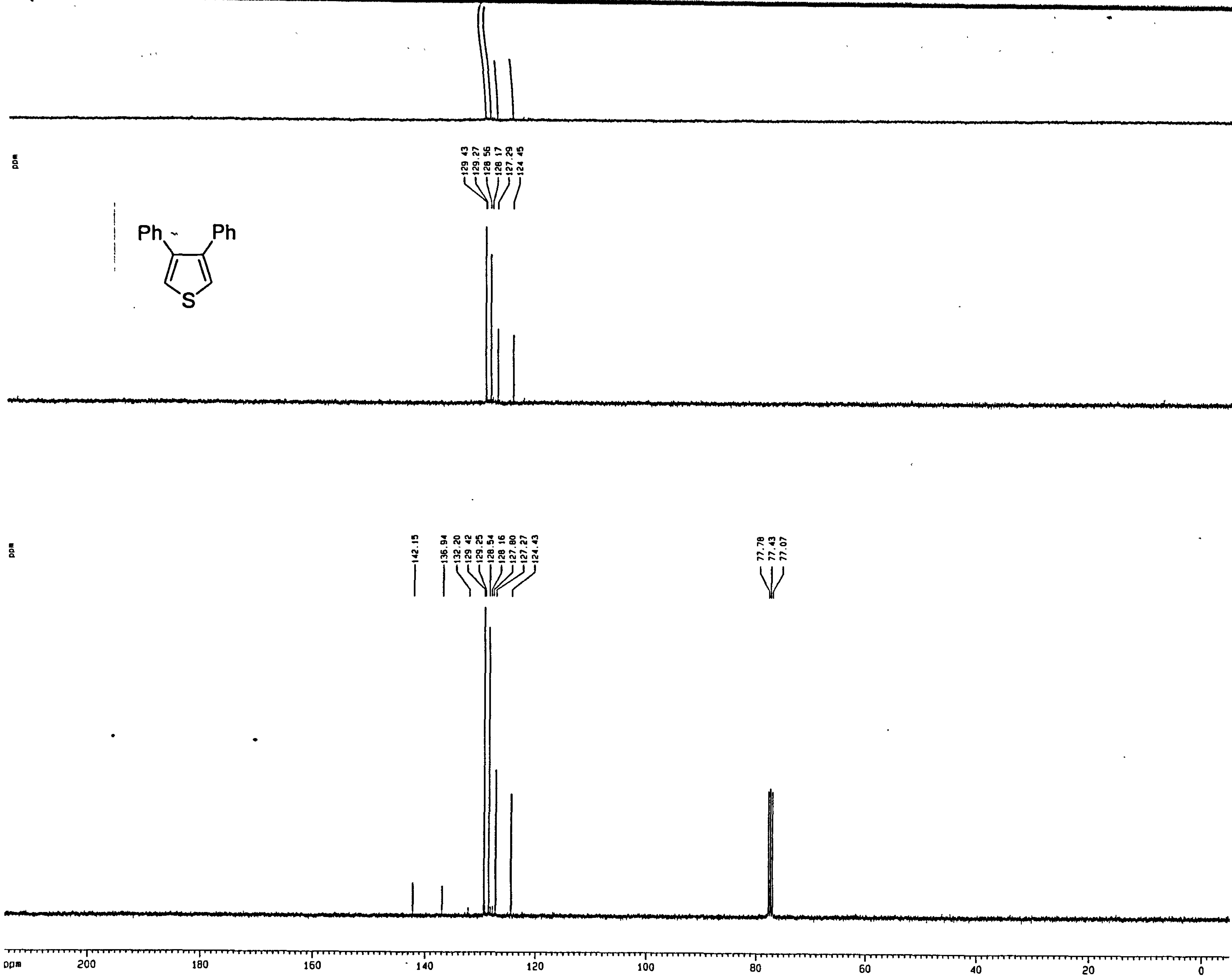
F2 - Acquisition Parameters
Date_ 20010602
Time 16.37
INSTRUM AV360
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 7440.476 Hz
FIDRES 0.113533 Hz
AQ 4.4040694 sec
RG 456.1
DW 67.200 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 11.25 usec
PL1 3.00 dB
SFO1 360.1322240 MHz

F2 - Processing parameters
SI 32768
SF 360.1300377 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 35.00 cm
CY 21.50 cm
F1P 7.362 ppm
F1 2651.27 Hz
F2P 7.039 ppm
F2 2535.01 Hz
PPMCM 0.00922 ppm/cm
HZCM 3.32164 Hz/cm

c13cpdno.k CDCl3 {C:\bruker\xwin-nmr} ap 15



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EXPNO 5
PROCNO 1

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Time 1.37
INSTRUM AV360
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 640
DS 4
SWH 27173.912 Hz
FIDRES 0.414641 Hz
AQ 1.2059124 sec
RG 14596.5
DW 18.400 usec
DE 6.00 usec
TE 300.0 K
D1 0.01000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

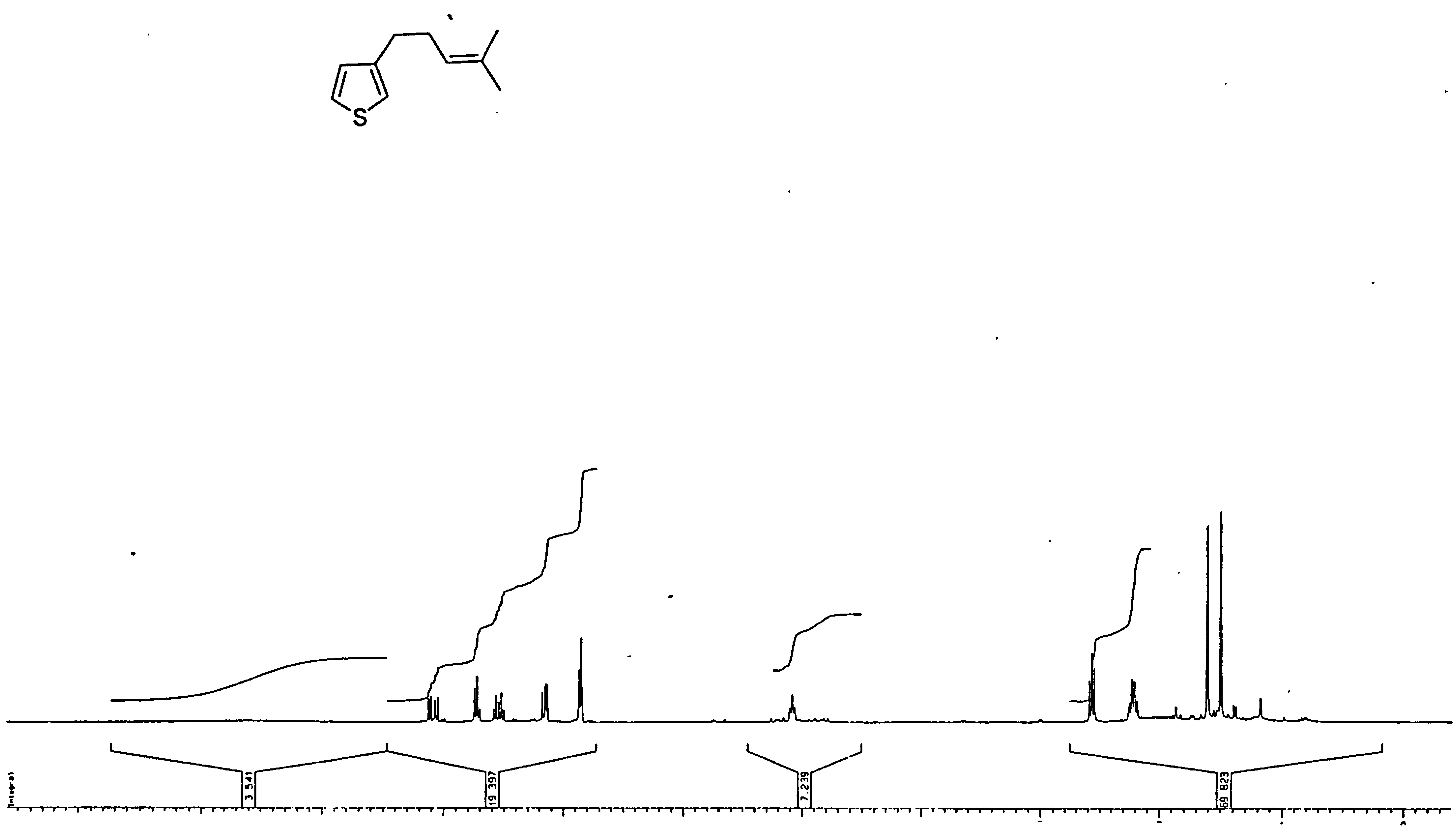
======== CHANNEL f1 ========
NUC1 13C
P1 5.88 usec
PL1 3.00 dB
SFO1 90.5646860 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 87.00 usec
PL2 3.00 dB
PL12 22.00 dB
PL13 120.00 dB
SFO2 360.1314405 MHz

F2 - Processing parameters
SI 32768
SF 90 5547250 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 35.00 cm
CY 8.70 cm
F1P 215.000 ppm
F1 19469.27 Hz
F2P -5.000 ppm
F2 -452.77 Hz
PPMCM 6.28571 ppm/cm
HZCM 569 20111 Hz/cm

proton.k C6D6 {C:\bruker\xwin-nmr} ap 56



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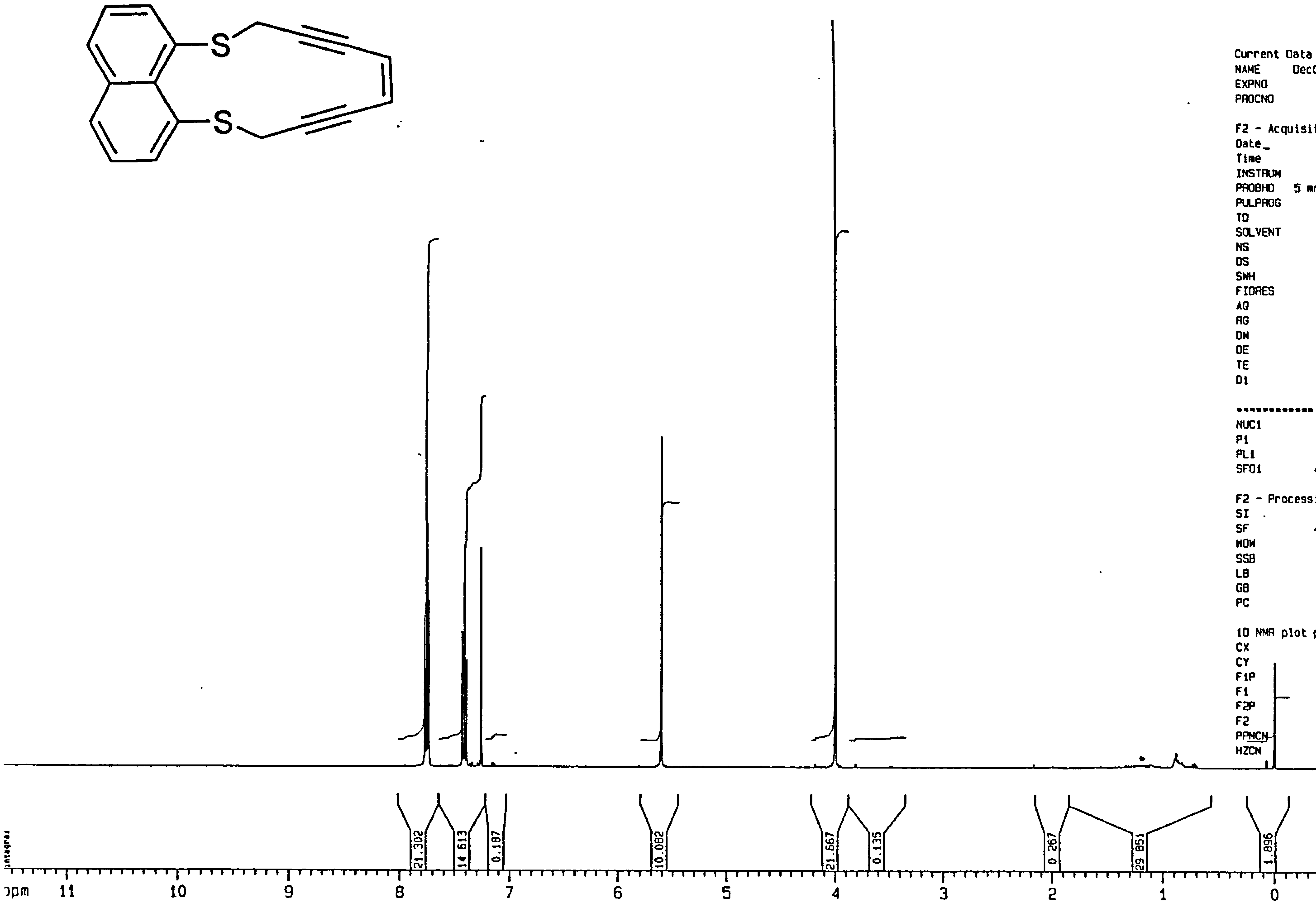
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20010712
Time 18.47
INSTRUM AV360
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT C6D6
NS 16
DS 2
SWH 7440.476 Hz
FIDRES 0.113533 Hz
AQ 4.4040694 sec
RG 90.5
DW 67.200 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 11.25 usec
PL1 3.00 dB
SFO1 360.1322240 MHz

F2 - Processing parameters
SI 32768
SF 360.1300506 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 35.00 cm
CY 21.50 cm
F1P 11.600 ppm
F1 4177.51 Hz
F2P -0.400 ppm
F2 -144.05 Hz
PPMCM 0.34286 ppm/cm
HZCM 123.47315 Hz/cm



Current Data Parameters
NAME Dec01-2000-4-49
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20001201
Time 18.17
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 512
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

============ CHANNEL f1 ==========
NUC1 1H
P1 8.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

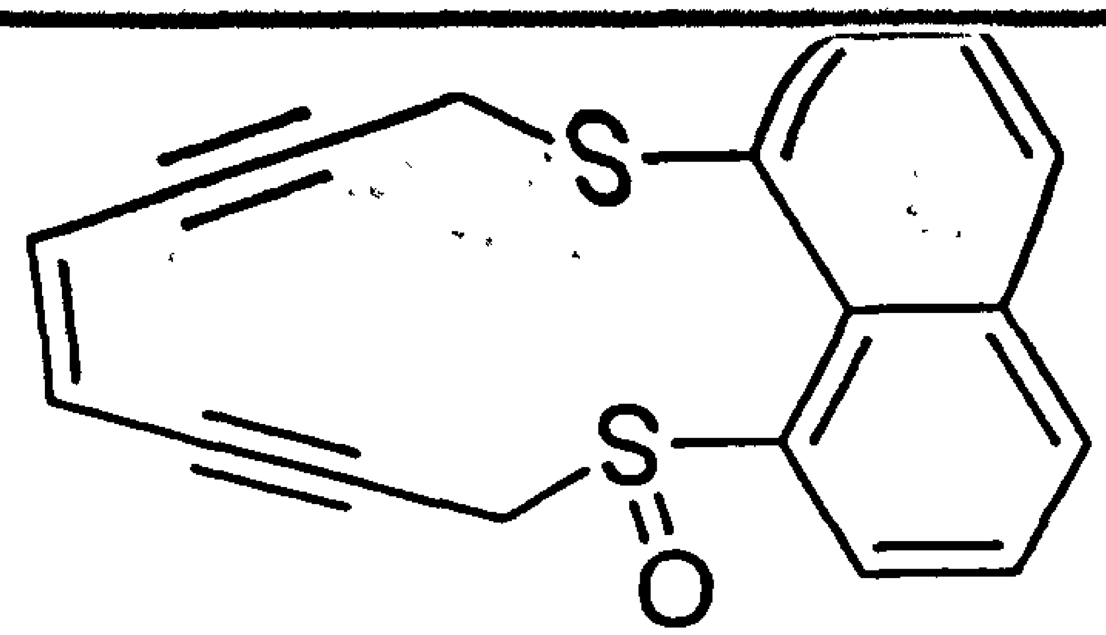
F2 - Processing parameters
SI 32768
SF 400.1300209 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 6.00

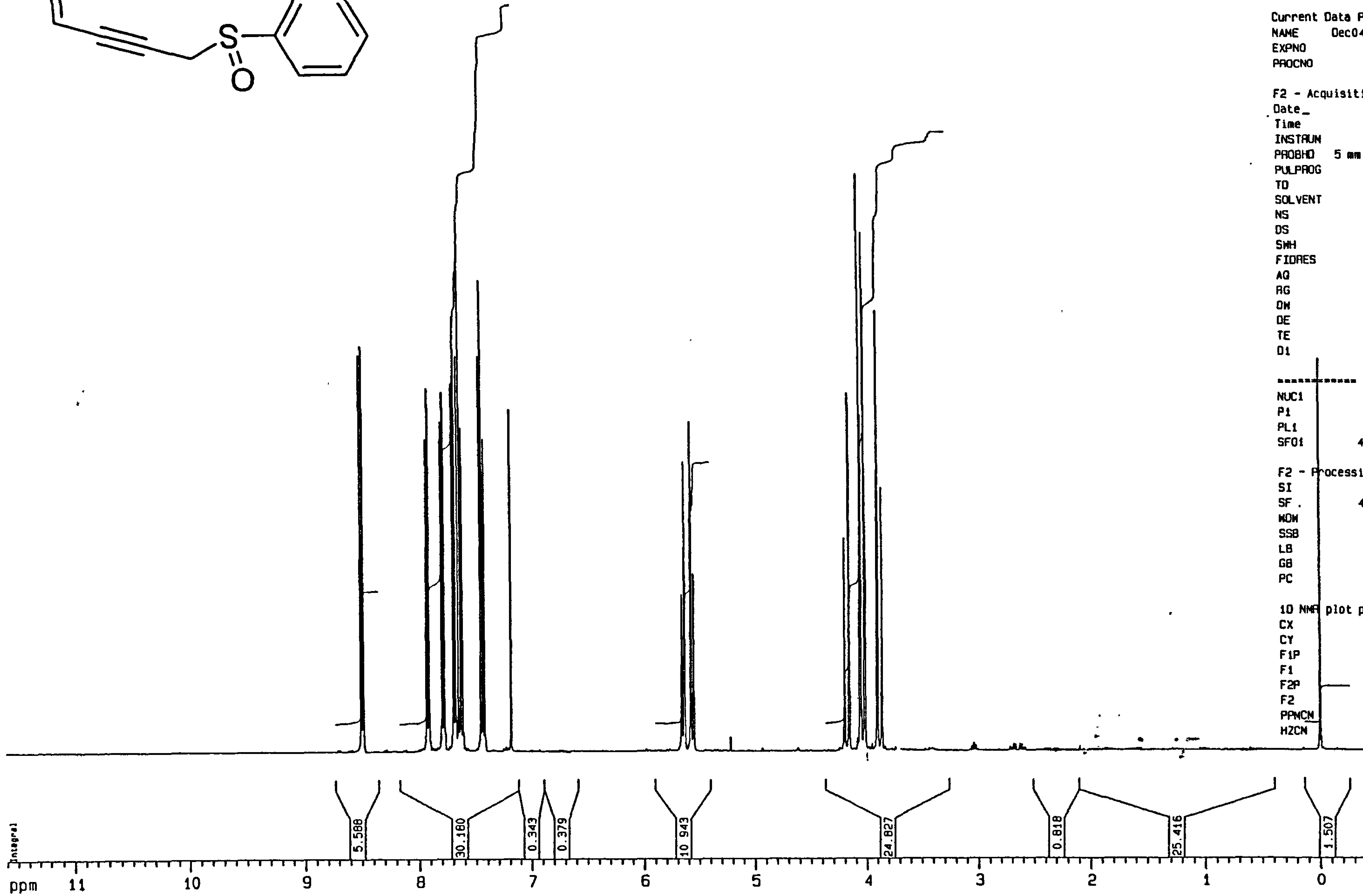
1D NMR plot parameters
CX 24.50 cm
CY 14.00 cm
F1P 11.600 ppm
F1 4641.51 Hz
F2P -0.400 ppm
F2 -160.05 Hz
PPMCM 0.48980 ppm/cm
HZCM 195.98207 Hz/cm

AP288A

PROTON_kcl CDCl3 {C:\u} General 49


AP203M 13C {1H}
BRUKER
PPM
JN0717.002
DATE 7-6-0
TIME 18:45
SF 90.556
SY 67.0
O1 66400.000
SI 65536
TD 65536
SW 23809.524
HZ/PT .727
PW 1.8
RD 0.0
AQ 1.376
RG 400
NS 520
TE 295
O2 .5500.000
DP 20H CPD
LB 2.000
GB 0.0
CX 40.00
CY 8.00
F1 198.006P
F2 -1.997P
HZ/CM 452.786
PPM/CM 5.000
SR 55758.76
134.810
133.182
129.660
125.672
120.902
94.520
82.188
77.480
77.067
76.714
28.528
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
PPM





Current Data Parameters
NAME Dec04-2000-4-19
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20001204
Time 14.25
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 256
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

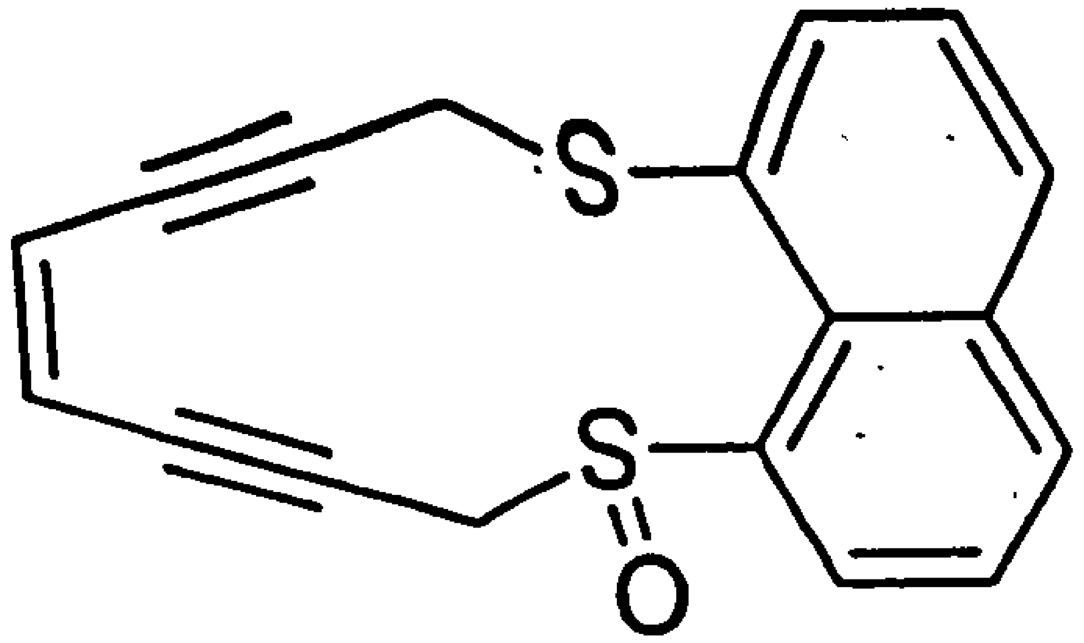
============ CHANNEL f1 ==========
NUC1 1H
P1 8.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

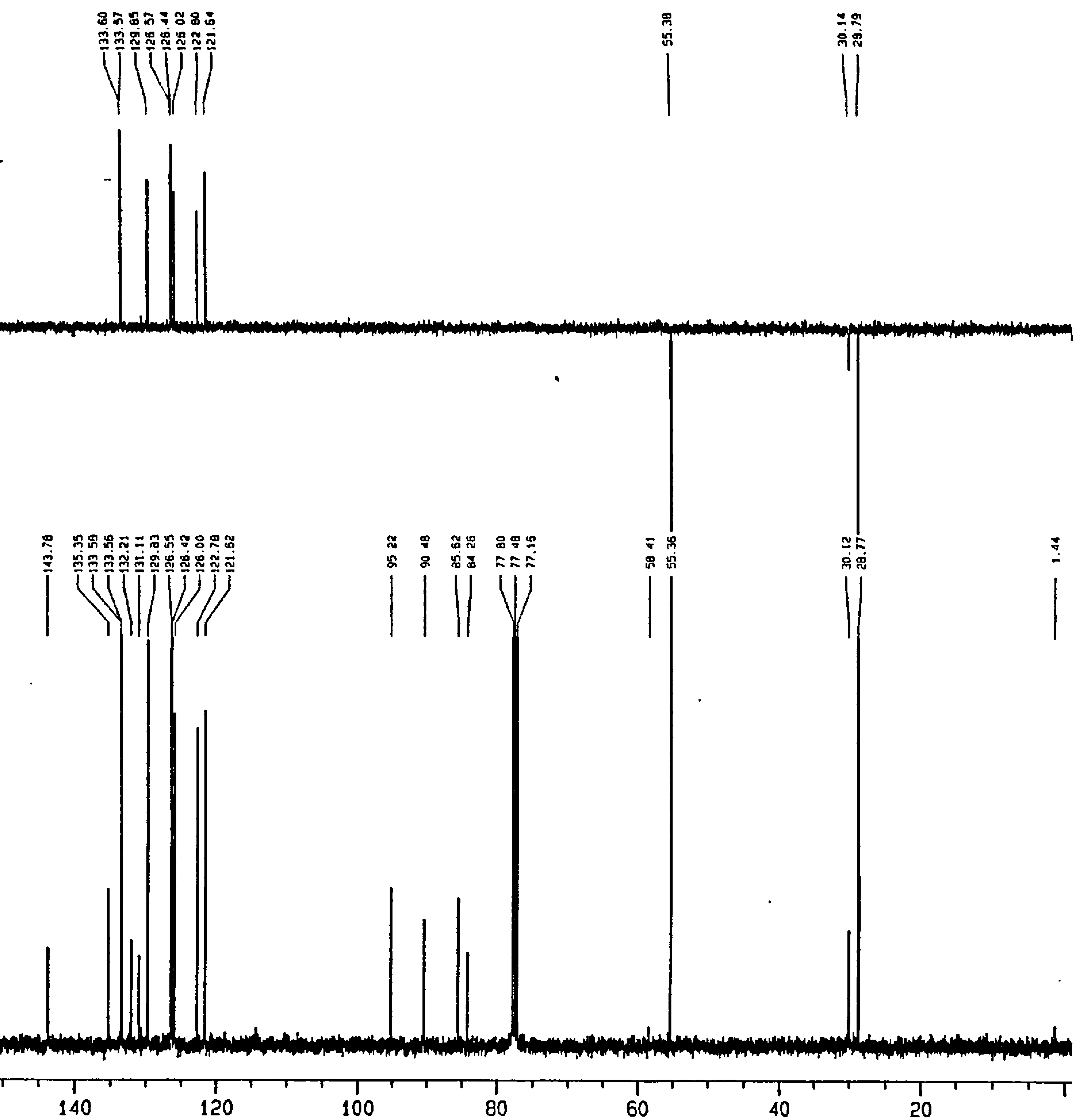
F2 - Processing parameters
SI 32768
SF 400.1300486 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 6.00

1D NMR plot parameters
CX 24.50 cm
CY 14.00 cm
F1P 11.600 ppm
F1 4641.51 Hz
F2P -0.400 ppm
F2 -160.05 Hz
PPMCM 0.48980 ppm/cm
HZCM 195.98207 Hz/cm

AP 288C

PROTON_kcl CDC13 {C:\u} General 19





AP 288C

C13CPD_kcl CDCl3 {C:\u} General 19

Current Data Parameters
NAME Dec04-2000-4-19
EXPNO 11
PROCNO 1

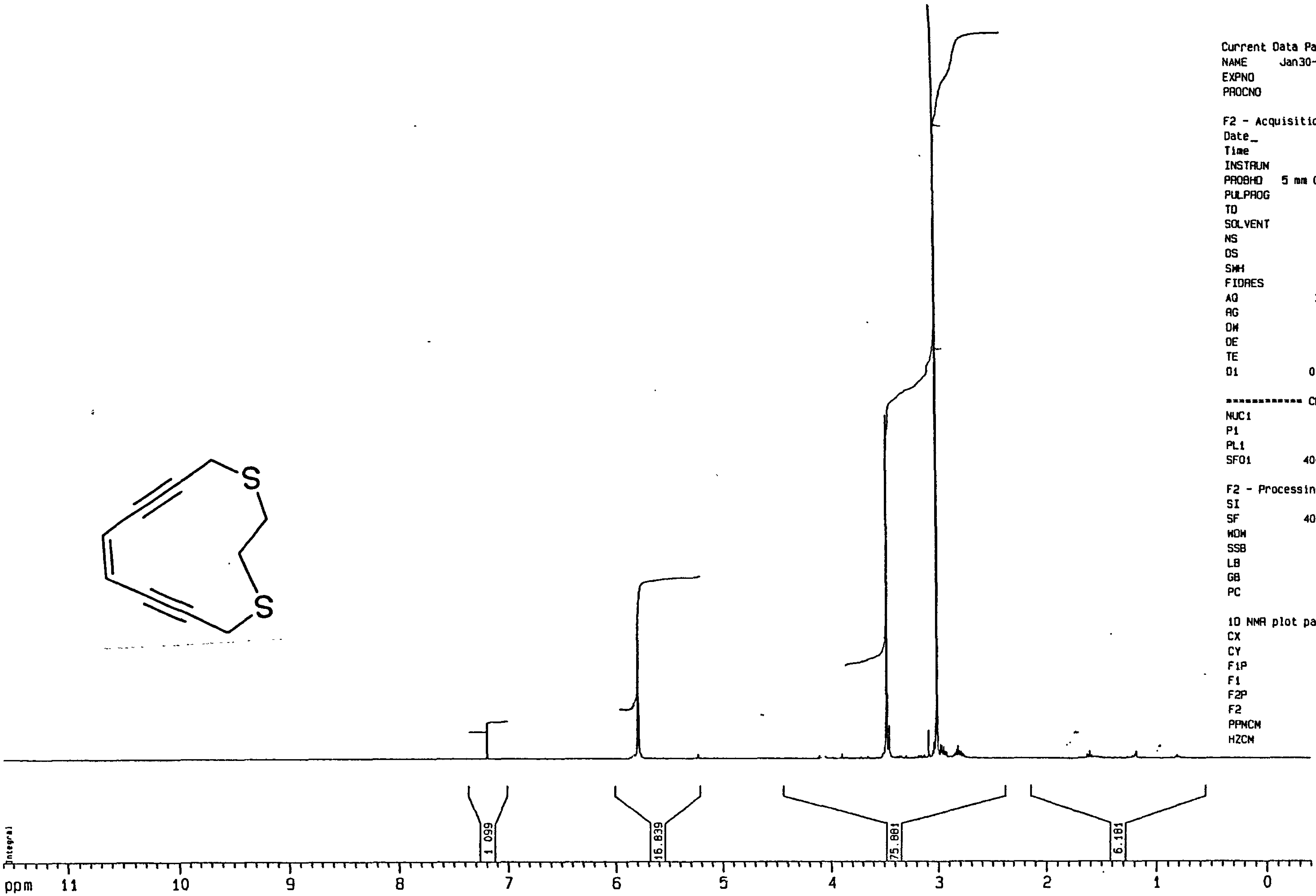
F2 - Acquisition Parameters
Date_ 20001204
Time 14.35
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 30120.482 Hz
FIDRES 0.459602 Hz
AQ 1.0879476 sec
RG 1149.4
DW 16.600 usec
DE 6.00 usec
TE 300.0 K
D1 0.01000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

============ CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 6.00 dB
SFO1 100.6237964 MHz

============ CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 82.00 usec
PL2 0.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 23.00 cm
CY 6.30 cm
F1P 220.000 ppm
F1 22134.80 Hz
F2P -1.000 ppm
F2 -100.61 Hz
PPMCM 9.60870 ppm/cm
HZCM 966.75708 Hz/cm



Current Data Parameters
NAME Jan30-2001-4-3
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20010130
Time 10.57
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 256
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

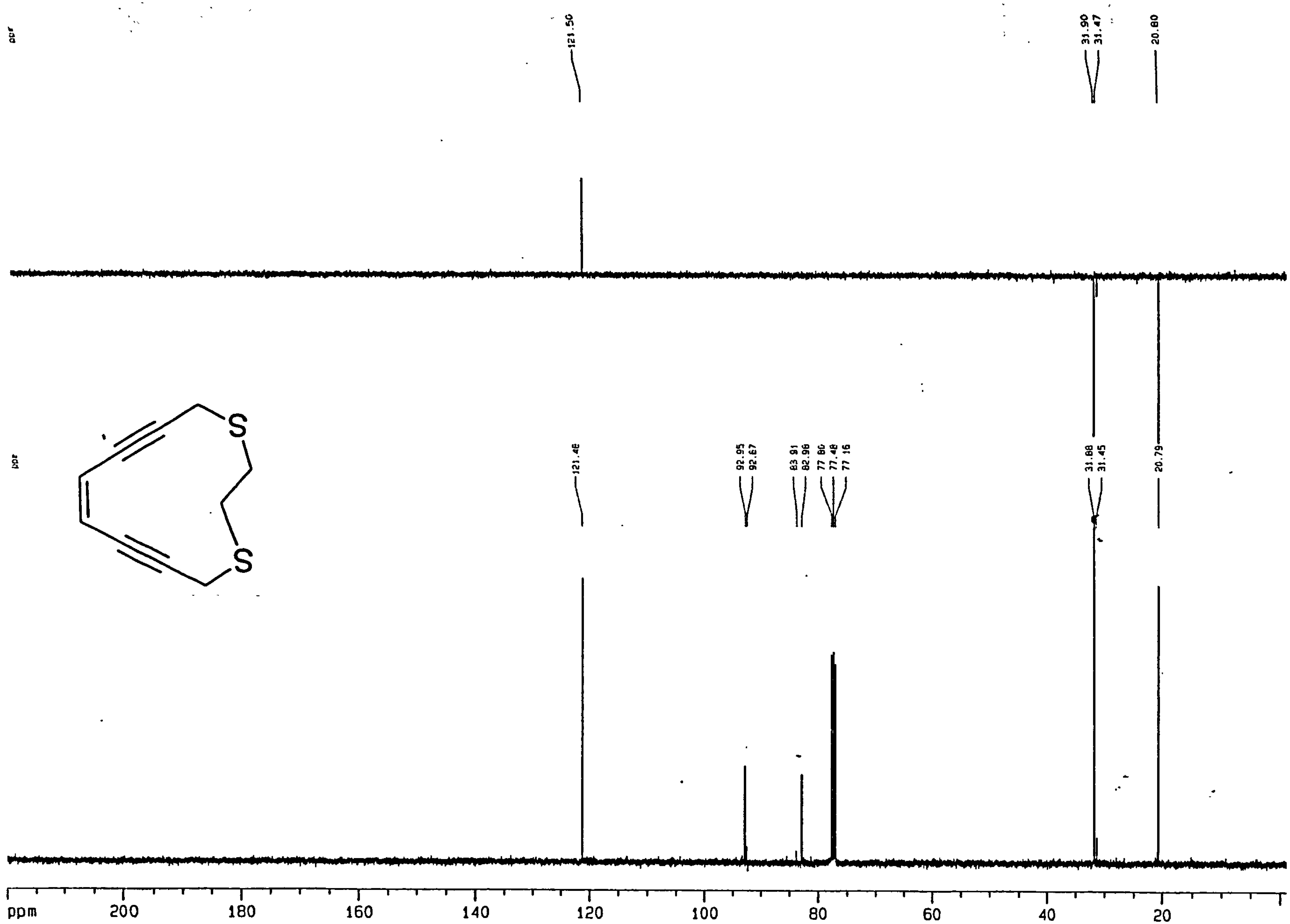
============ CHANNEL f1 ==========
NUC1 1H
P1 8.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300442 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 6.00

1D NMR plot parameters
CX 24.50 cm
CY 14.00 cm
F1P 11.600 ppm
F1 4641.51 Hz
F2P -0.400 ppm
F2 -160.05 Hz
PPMCM 0.48980 ppm/cm
HZCM 195.98207 Hz/cm

AP 306

PROTON_kcl CDCl3 {C:\u} General 3



AP 306

C13CPD_kcl CDCl3 {C:\u} General 3

Current Data Parameters

NAME	Jan30-2001-4-3
EXPNO	11
PROCNO	1

F2 - Acquisition Parameters

Date_	20010130
Time	11.07
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	30120.482 Hz
FIDRES	0.459602 Hz
AQ	1.0879476 sec
RG	181
DW	16.600 usec
DE	6.00 usec
TE	300.0 K
D1	0.01000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

============ CHANNEL f1 =======

NUC1	13C
P1	8.50 usec
PL1	6.00 dB
SFO1	100.6237964 MHz

============ CHANNEL f2 =======

CPDPRG2	waltz16
NUC2	1H
PCPD2	82.00 usec
PL2	0.00 dB
PL12	20.00 dB
PL13	20.00 dB
SFO2	400.1316005 MHz

F2 - Processing parameters

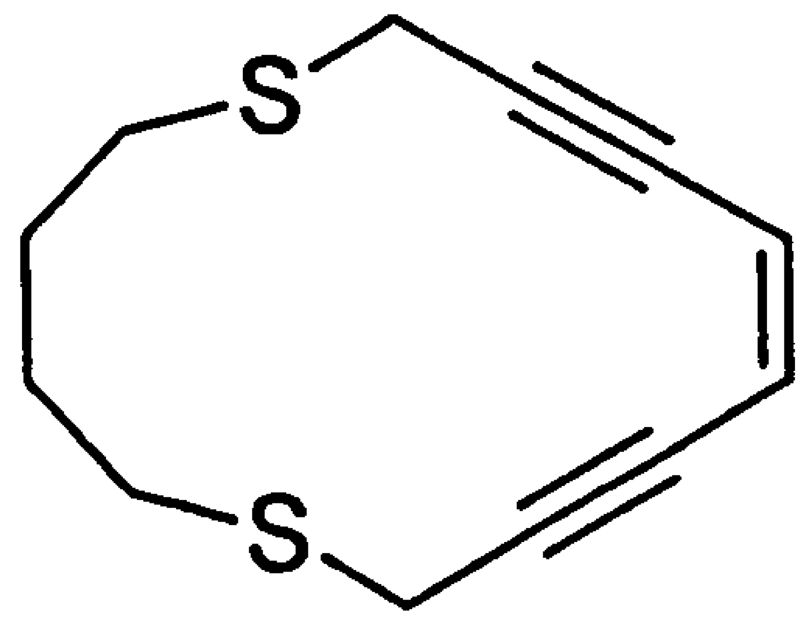
SI	32768
SF	100.6127290 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

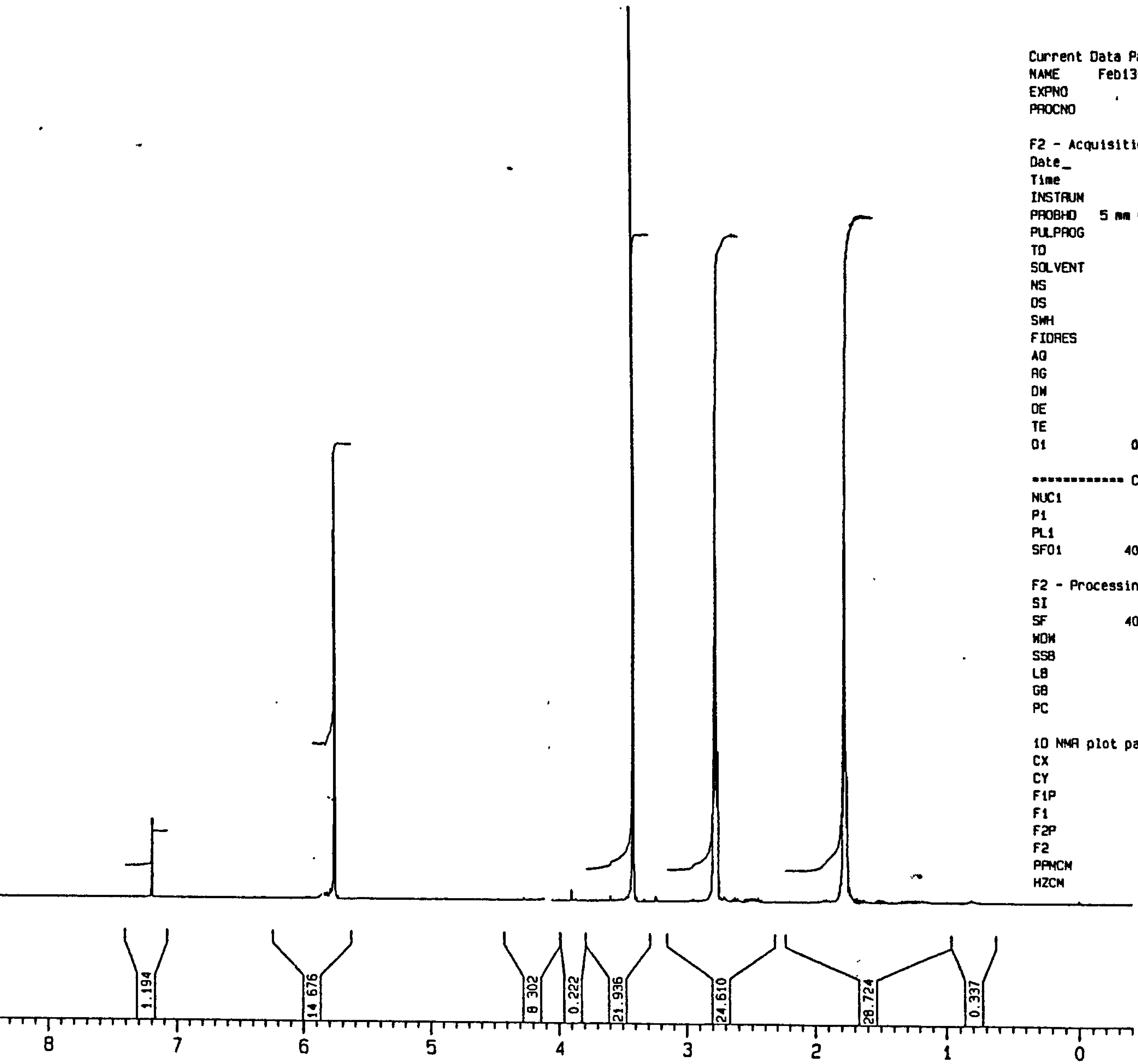
1D NMR plot parameters

CX	23.00 cm
CY	6.30 cm
F1P	220.000 ppm
F1	22134.80 Hz
F2P	-1.000 ppm
F2	-100.61 Hz
PPMCM	9.60870 ppm/cm
HZCM	966.75708 Hz/cm


S
S
9.00
8.00
7.50
7.00
6.00
5.00
4.50
PPM
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0


AP.136 13C (1H)
PPM





Current Data Parameters
NAME Feb13-2001-4-59
EXPNO 10
PROCNO 1

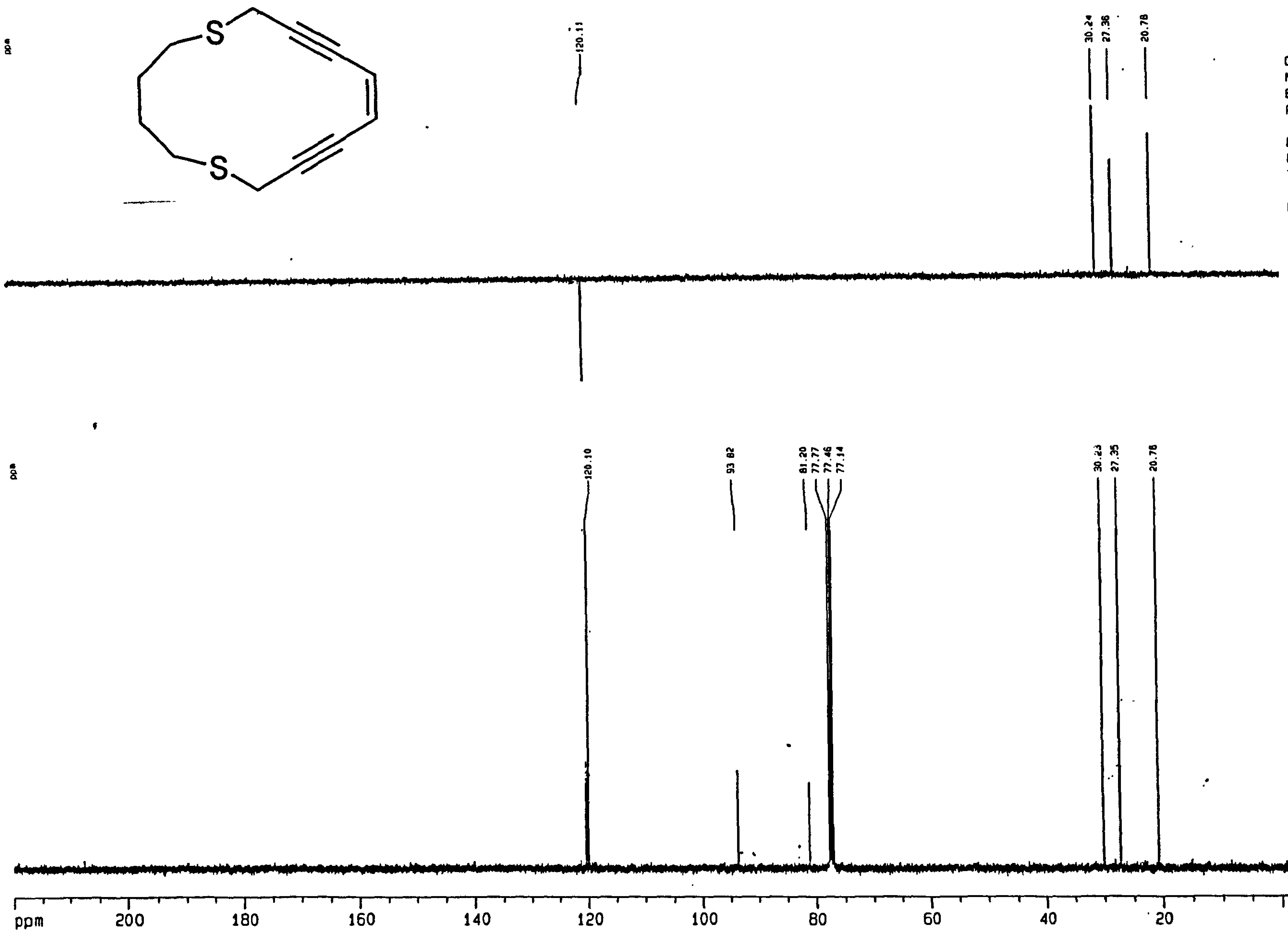
F2 - Acquisition Parameters
Date_ 20010213
Time 18.08
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 256
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

============ CHANNEL f1 ==========
NUC1 1H
P1 8.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300464 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 6.00

1D NMR plot parameters
CX 24.50 cm
CY 14.00 cm
F1P 11.600 ppm
F1 4641.51 Hz
F2P -0.400 ppm
F2 -160.05 Hz
PPMCM 0.48980 ppm/cm
HZCM 195.98207 Hz/cm

AP315B
PROTON kcl CDCl3 {C:\u} General 59



AP315B

C13CPD_kcl CDCl3 {C:\u} General 59

Current Data Parameters
NAME Feb13-2001-4-59
EXPNO 11
PROCNO 1

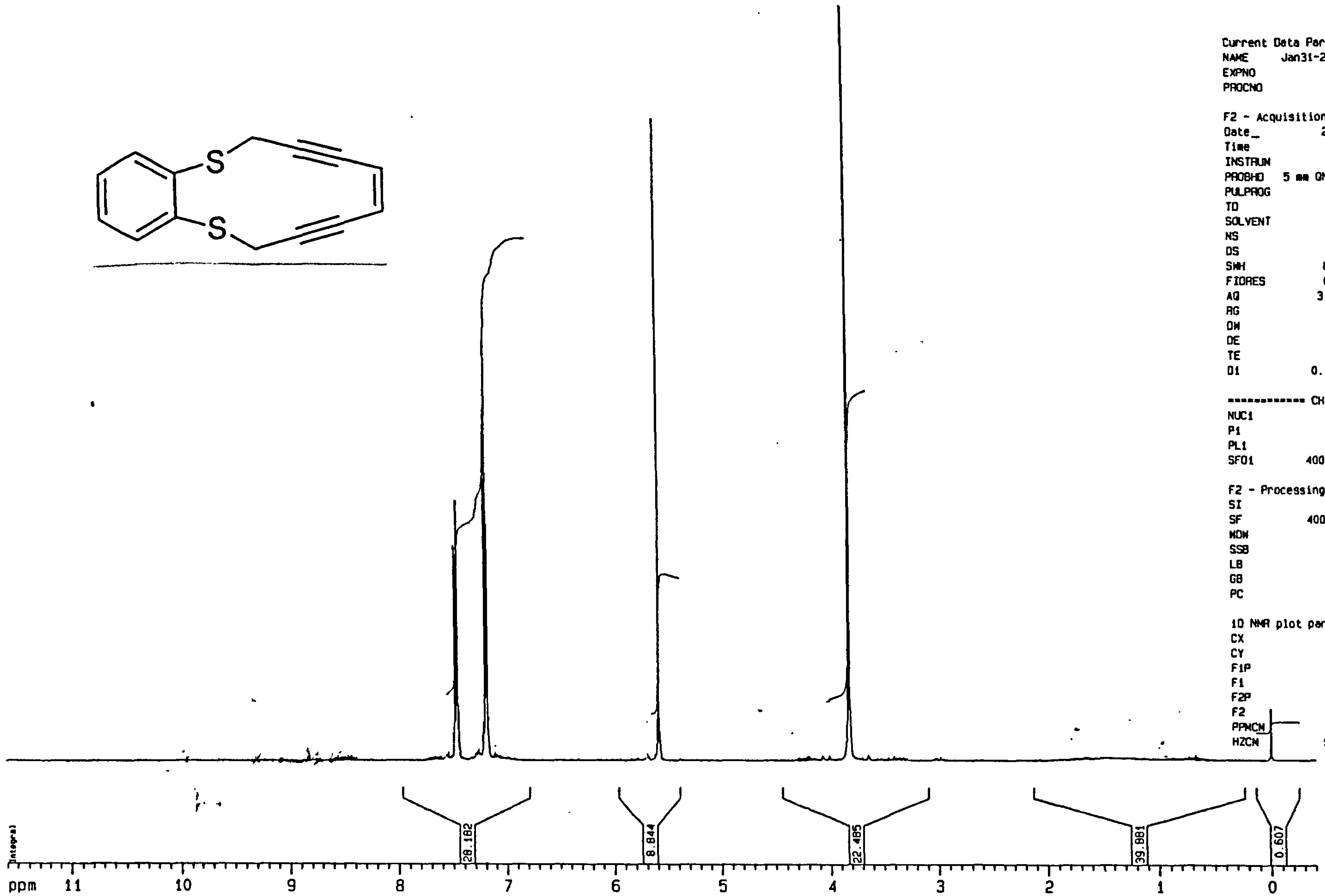
F2 - Acquisition Parameters
Date_ 20010213
Time 18.27
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 30120.482 Hz
FIDRES 0.459602 Hz
AQ 1.0879476 sec
RG 812.7
DW 16.600 usec
DE 6.00 usec
TE 300.0 K
D1 0.01000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

============ CHANNEL f1 ======
NUC1 13C
P1 8.50 usec
PL1 6.00 dB
SFO1 100.6237964 MHz

============ CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 82.00 usec
PL2 0.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 23.00 cm
CY 6.30 cm
F1P 220.000 ppm
F1 22134.80 Hz
F2P -1.000 ppm
F2 -100.61 Hz
PPMCM 9.60870 ppm/cm
HZCM 966.75708 Hz/cm



Current Data Parameters
NAME Jan31-2001-4-59
EXPNO 10
PROCNO 1

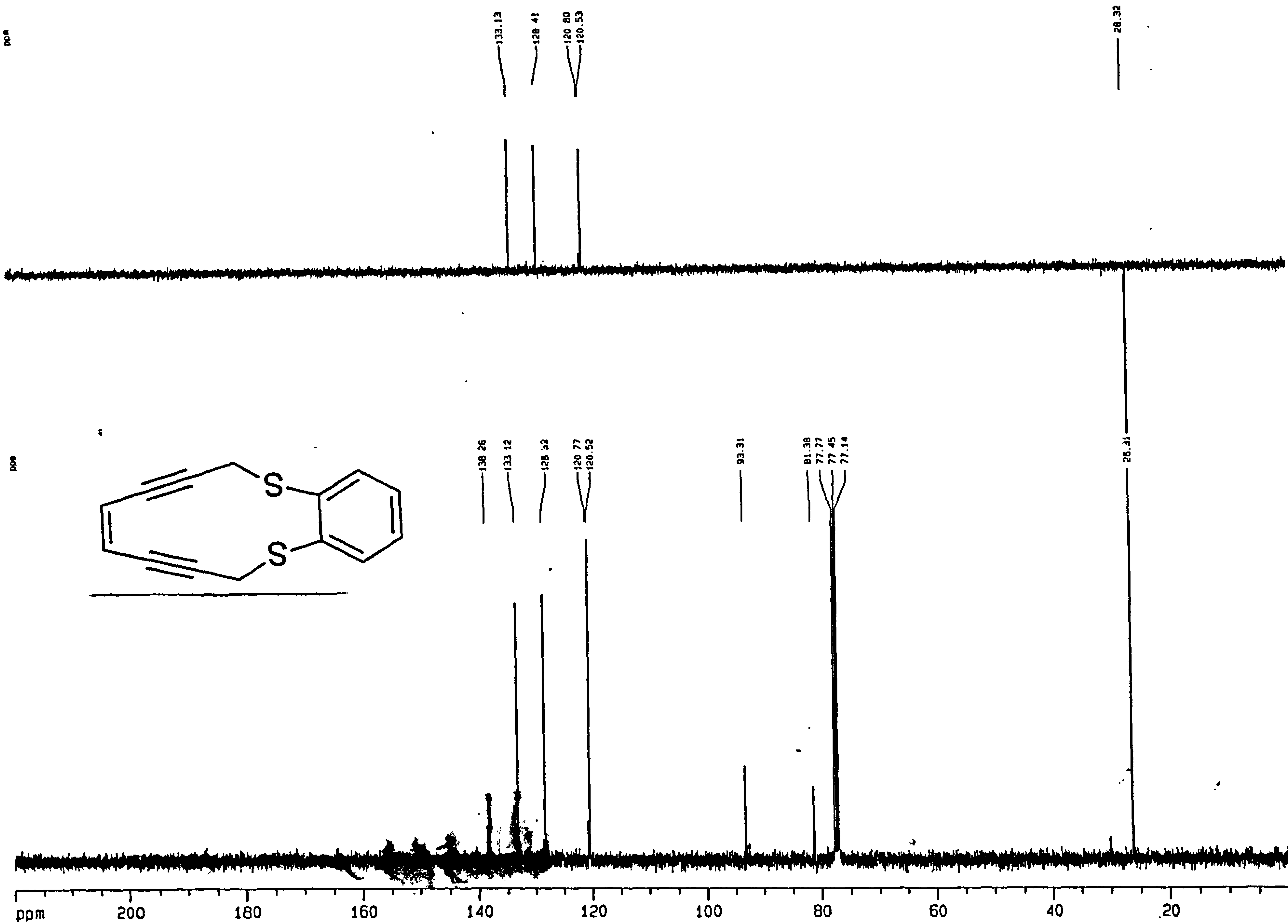
F2 - Acquisition Parameters
Date_ 20010201
Time 10.01
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

============ CHANNEL f1 ==========
NUC1 1H
P1 8.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300478 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 6.00

1D NMR plot parameters
CX 24.50 cm
CY 14.00 cm
F1P 11.600 ppm
F1 4641.51 Hz
F2P -0.400 ppm
F2 -160.05 Hz
PPMCM 0.48980 ppm/cm
HZCM 195.98207 Hz/cm

AP307
PROTON_kcl CDCl3 {C:\u} General 59



AP307

C13CPD_kc1 CDC13 {C:\u} General 59

Current Data Parameters
NAME Jan31-2001-4-59
EXPNO 11
PROCNO 1

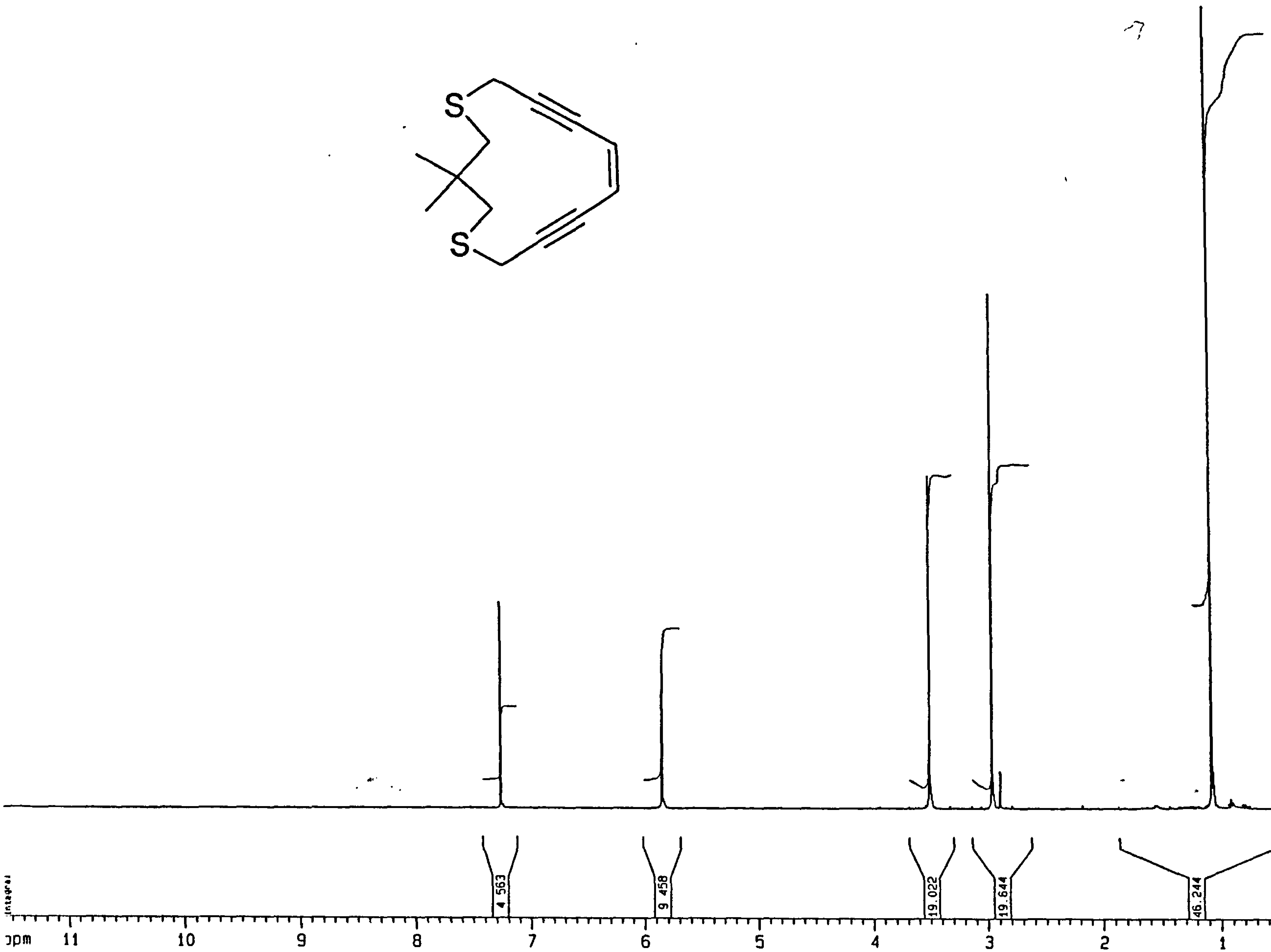
F2 - Acquisition Parameters
Date_ 20010201
Time 10.21
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 1024
DS 4
SWH 30120.482 Hz
FIDRES 0.459602 Hz
AQ 1.0879476 sec
RG 512
DW 16.600 usec
DE 6.00 usec
TE 300.0 K
D1 0.01000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

============ CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 6.00 dB
SFO1 100.6237964 MHz

============ CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 82.00 usec
PL2 0.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 23.00 cm
CY 6.30 cm
F1P 220.000 ppm
F1 22134.80 Hz
F2P -1.000 ppm
F2 -100.61 Hz
PPMCM 9.60870 ppm/cm
HZCM 966.75708 Hz/cm



Current Data Parameters
NAME Jan10-2001-4-46
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20010110
Time 18.37
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 645.1
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

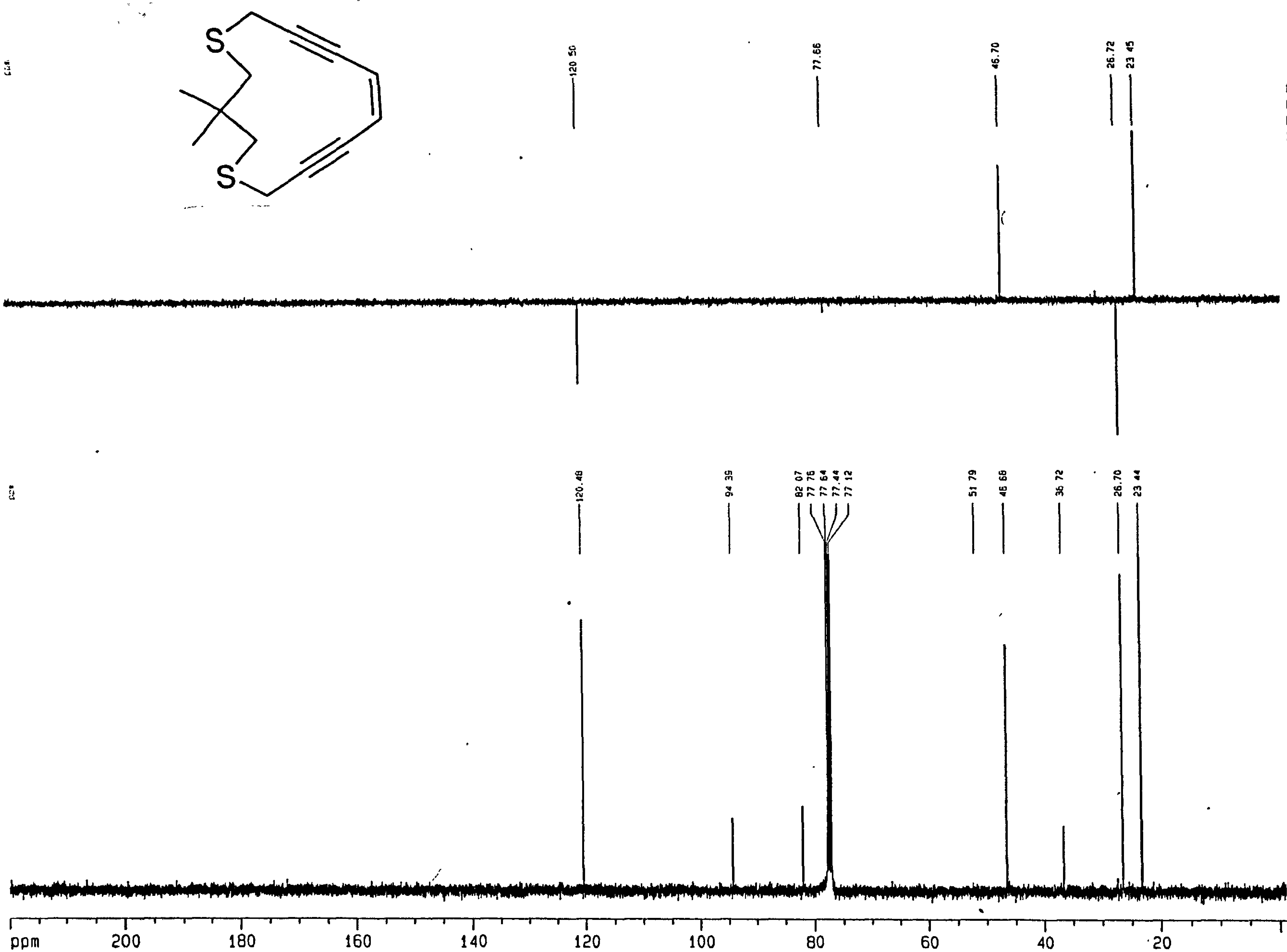
============ CHANNEL f1 =========
NUC1 1H
P1 8.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300200 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 6.00

1D NMR plot parameters
CX 24.50 cm
CY 14.00 cm
F1P 11.600 ppm
F1 4641.51 Hz
F2P -0.400 ppm
F2 -160.05 Hz
PPMCM 0.48980 ppm/cm
HZCM 195.98206 Hz/cm

AP296

PROTON kcl CDCl3 {C:\u} General 46



AP296

C13CPD_kcl CDCl3 {C:\u} General 51

Current Data Parameters
NAME Jan11-2001-4-51
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20010111
Time 19.48
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 4096
DS 4
SWH 30120.482 Hz
FIDRES 0.459602 Hz
AQ 1.0879476 sec
RG 1824.6
DW 16.600 usec
DE 6.00 usec
TE 300.0 K
D1 0.01000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

============ CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 6.00 dB
SFO1 100.6237964 MHz

============ CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 82.00 usec
PL2 0.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 23.00 cm
CY 6.30 cm
F1P 220.000 ppm
F1 22134.80 Hz
F2P -1.000 ppm
F2 -100.61 Hz
PPMCM 9.60870 ppm/cm
HZCM 966.75708 Hz/cm

AP.133

9.50
9.00
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
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PPM
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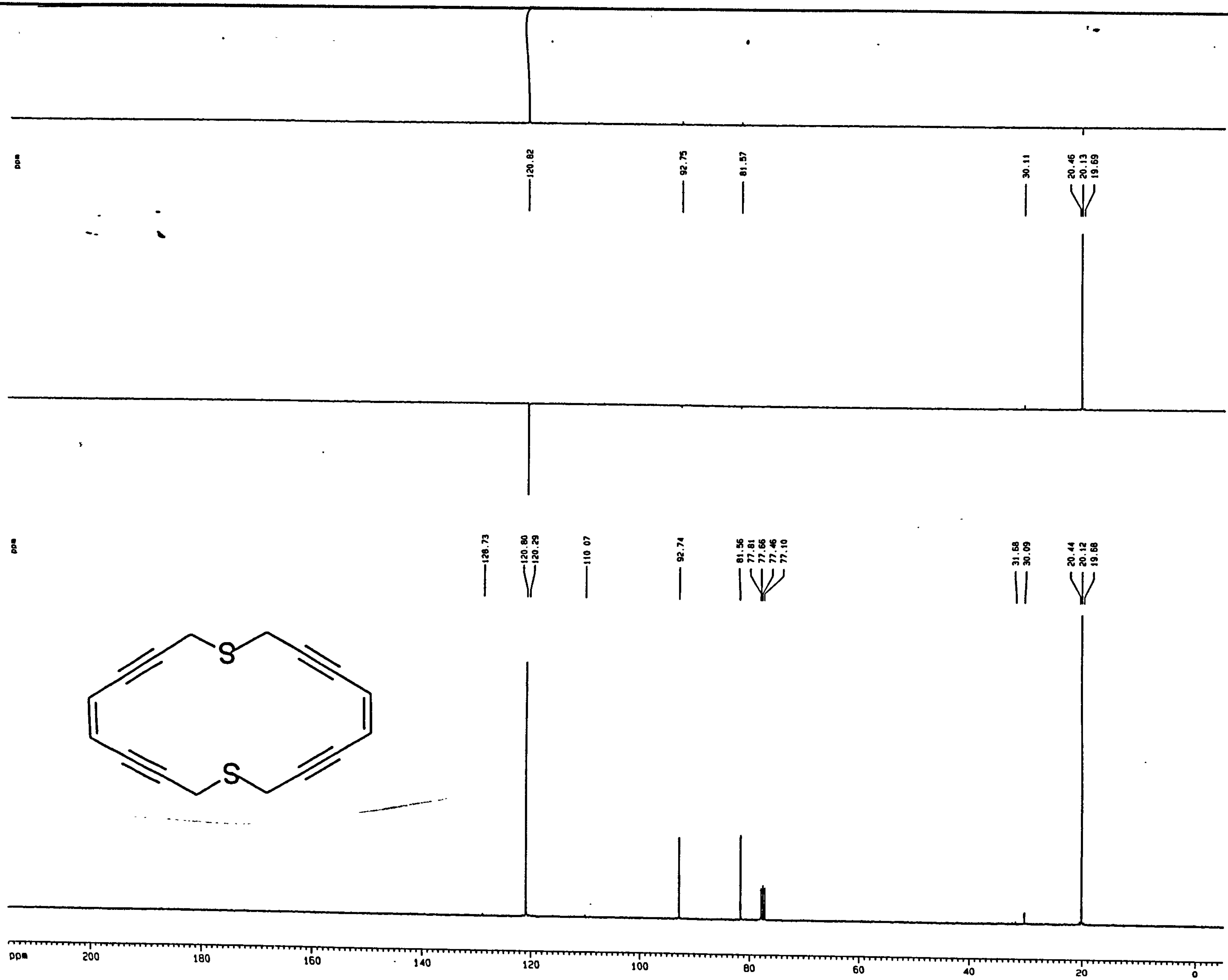
1.50
1.00
.50
0.0



Current Data Parameters
NAME ap-Jul24-2001
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20010724
Time 23.18
INSTRUM AV360
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 640
DS 4
SWH 27173.912 Hz
FIDRES 0.414641 Hz
AQ 1.2059124 sec
RG 1448.2
DW 18.400 usec
DE 6.00 usec
TE 300.0 K
D1 0.01000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

======== CHANNEL f1 ========
NUC1 13C
P1 5.88 usec
PL1 3.00 dB
SFO1 90.5646860 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 87.00 usec
PL2 3.00 dB
PL12 22.00 dB
PL13 120.00 dB
SFO2 360.1314405 MHz

F2 - Processing parameters
SI 32768
SF 90.5547250 MHz
WDW EM
SSB 0
LB 1 00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 35.00 cm
CY 8.70 cm
F1P 215.000 ppm
F1 19469.27 Hz
F2P -5.000 ppm
F2 -452.77 Hz
PPMCM 6.28571 ppm/cm
HZCM 569.20111 Hz/cm

C13cpdno.k CDCl3 (C:\bruker\xwin-nmr) ap 30